X

"D I P H T H E R I A."

THESIS

for the

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by:-

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DIPHTHERIA.

(Diphtheritis; Angina Maligna; Croup.)

DEFINITION. -
An acute specific contagious disease, due to the Klebs - Löffler bacillus, characterised by the formation, upon the mucons membrane of the pharynx, nose, larynx, or existing cutaneous abrasions, of a yellowish or grayish white pellicle consisting of a fibrinous exudation, and producing in the majority of instances severe prostration or grave complications.

HISTORY.

And Geographical distribution.

That diphtheria is one of the oldest epidemic diseases of the human race cannot be gainsaid: a disease of a similar nature is even mentioned in the Talmud("Talmud Babylonicum," Tract Berachoth 8a, Sabbath 33b, Taänis 31b); and in the Writing of Hippocrates, especially in "Liber de dentitione" (20, seq. ed., Littré VLLL, 546-48) and in "Liber epidemiorum"(VI, Sect. VII,1, ed. cit, V, 330) where the reference is to an epidemic of cough in Perinthos, the same being specially commented on by Littré ("Oeuvres compl. de Hippokrate," X, 1, and "Gaz. méd. de Paris," 1861, p.353). The first complete description of the disease, however, is to be found in Writings

of the Greek physicians Aretaeus ("De causis et signis acut. morb.," lib.1, cap. IX, ed. Kühn, p. 17) and Aetius ("Tetrabiblion," II, sermo IV, cap. XLVI, ed. Stephanus, p. 397), about the year A.D. 50; a passage, quoted by Häser ("Histor - pathol. Untersuch.," 274) from Archigenes and the fourth book of Oribasius (Mai - "Collect. auct. classic. e. Vatic. cod. Edita," IV, 197) containing a mere superficial description of malignant sore throat. Both Aretaeus and Aetius describe the disease as being one that occurred mostly amongst children, and, at their time, in Syria and Egypt. Aetius's account is of more than passing interest in it contains special reference to paralysis of the muscles of deglutition, thus: "Crustosa et pestilentia tonsillarum ulcera, ut plurimum nullo praecedente tonsillarum fluxu incipiunt, aliquando autem a consuetis fieri inflammationibus, maxime efferatis, perficiuntur. Fiunt autem frequentissime pueris atque etiam aetate jam perfectis, maxime iis qui vitiosis humoribus abundant, in iis qui vere contingere solent pestilentibus constitutionibus. In pueris vero oris ulcere quod aplittiam vocant, praecedente omnino perficiuntur. Sunt autem partim alba, maculis similia, partim cinereo colore, aut similia crustis, quae ferro inducuntur. Accidit autem aegris siccatas in transglutiendo, et suffocatio coacervatim incidit. Et febrium quoque curam habere convenit (vehementes enim incidere solent) atque in repurgandis explanandisque ulceribus maxime sollicitum esse; convulsionem enim infantes plurimi passi sunt in ulcerum repurgatione; aliqui

vero via transglutiendi exsiecata, sunt strangulati. Sunt enim quibis corrvduntur gurgulationes, atque ubi diutius perstiterint ulcerationes et in profundum proserpserint, cicratici jam inducta, adstrict - iorem vocem edunt, reflictitorque ipsis potus in ipsas nares; nam et ego puellam novi quae post quadragesimum tandem diem consumpta est, quum se jam a morbo recolligeret. Verum at septimum usque diem plurimi periclinantur."

The writings, moreover, of both the mediaval physicians of the West and of Arabia contain numerous references to a fatal form of "Angina," probably not diphtheria at all, but secondary faucial affections complicating some other infectious malady. Some of the cases reported about this period are usually believed to have been true diphtheria. St. Denis, ("Chronicles") for instance, writing about the year 580, makes mention of a "pest" known as "esquinancie," corresponding to "squinantia," a name subsequently applied to diphtheria. About three centuries later (A.D.85 6), Baronius ("Annal. ecclesiast.") describes a throat affection of a diphtheritic nature;- pestilentia faucium, qua fluxione guttur obstructum citam mortem inferret," - which was observed at Rome; at which city also an epidemic of the kind prevaled in 1004 - "Catarrhus descendens in fauces, meatus obstruens, sufficatos miseros homines confestim mori congebat." Writing about the year 1039, Cedrenus ("Comp. historiar.," Paris, 1647, II, 742) states that an epidemic, known as "Kunagxe" prevailed about that

time in some districts of the Byzantine Empire, and was attended by a frightful mortality. From the symptoms recorded, the disease could have been none other than diphtheria. The epidemic described, as prevalent in England, in 1339, by Short (Webster's "History of Epidemic and Pestilential Diseases," Hartford, 1779, I, 143) is interesting in that it mentions the great mortality of diphtheria amongst children, a point to which the other writers, quoted above, do not refer.

Coming down to the sixteenth century many accounts of the disease are extant. Thus, for the year 1517, one reads in the Chronicles (Frank von Wörd. - "Chronik fortges. von Calon. Ghönner," 3. I., 1585, II, 640; Basel chronicle of Wurstissen, 1580, p. 707; and "Schwytzer Chronik" of Stumpff, 1606, p.114a.) of an "unknown" sickness which seems to have devastated the Rhine districts, "so that men's tongues and throats were covered as with a fungus, and turned white, and they were neither able nor inclined to eat or drink from pains in the head not unattended with pestilential fever." This epidemic, in the same year, seems to have extended to Amsterdam, as Tyengius (cited by Foreest - "Observat. et curat. medicina," VI, lib. observat. II schol., Lugd. Bat., 1591, p.10), who at that time was actively engaged in combatting it, relates: "Ut quibus intra sex aut octo horas apta remedia non adhihebantur, ante sedecim aut viginti horas subito moriebantur. Erat autem materia in illo

morbo populari ita furiosa, ut uno momento tantam anhelitus difficultatem, cordis que augustiam et dolorem in collo pararet, ut aegrotus strangulari mox videretur." Sennert (Pract. Medicuiae," lib. II, pars i, cap.24, Wittenberg, 1654, p.94) reports that a somewhat similar diphtheritic affection prevailed in epidemic form throughout many of the German and Rhenish provinces in 1544 and 1545, where too, in 1564 and 1576, according to Weir ("Observat.," natural divinis characterismis," &c., Antwerp, 1575, II,44), and Pascal ("Mém. de méd. milit.," Alsace, 1841, LI,I), an epidemic of angina maligna proved very destructive to children, who were also suffered often from it than adults. Regarding it Weir remarks: "ob hanc causam quod eidem affecti primo die, nonnulli tertio aut quarto moriebantur, paucique ad septimum usque pertingebant."

Lib. T 3. Op. Amstelod. 1660, p. 910) Gemma (De

Regarding the great epidemics from the sixteenth to the eighteenth centuries, it seems that the first reliable account of angina maligna extant is one emanating from Spain, where the disease, under the name of "Garrotillo" (so called from the short stick used in strangling criminals to death) is stated to have been epidemic for thirty years, in direct continuity from 1583, to spread thereafter to various other regions. Relyingon the statement of Gutierrez de Angulo (cited by Morejon - "Histor Bibliogr. de la Medicina espanola," Madrid, 1843, II,211) that "tradudo del enfermedad del garrotillo," and in view also of his having practised all his life in the provine of Malago, the disease must have been prevalent

In Spain before this and been well known there under its popular designation of garrotillo. As well as Spain, the disease appears to have invaded Portugal, Italy and islands where it was observed in endemic form about the year 1618. The first part of Spain in which the disease appears was Saville - in 1583 - from whence it took about eight years to propagate itself over Andalusia (De Villa Real - "De Signis, causis, et curatione morbi suffocationis," libri III, compluti 1611. Gonzalez de Sepulveda - "Tratado sobre el garrotillo en el ano de 1606," s. l. e. a. Fontecha- "Disputiones med. de anginarum naturis, et de circa affectionem hisce temporibus vocatam Garrotillo," Compluti 1611. Cascales - "Liber de affetionibus puerorum, de morbillo illo, qui vulgariter garrotillo hispan. appellatur," Madr., 1611. Perez de Herrera - "Tract. de Essentia, causis, notis et precautione faucium et gutturis anginosorum morbi suffocantis garrotillo hispan. appellati," Madr., 1615. Nunnez de Lerena - "De gutturis et faucium ulceribus anginosis, Vulgo garrotillo," Sevilla, 1615. San Millan - "Parecer en que se trata, de la enfermeda que vulgarmente blaman garrotejo," Zaragoca, 1616. Soto - "Libro del conocimiento, de la enfermedad del garrotillo," Granada, 1616. Mercado - "Consult. med. lib. cons. XIV, " in Opp., Frankf., 1620, 134. "Charta imperiolis de morbo suffocativo, " Madrid, 1620. Tamajo - "Tratado breve de algebra y garrotillo," Madrid, 1621. Perra - "Polyanthea medicis speciosa," Madrid, 1625. Sola - "Del garrotillo sive de morbo suffocante," Sevilla, 1630. Heredia - "De morbis acutis," lib. II, sect. III, cap,5, Lyon, 1685 in Opp.

Antwerp, 1690, III, 100. Villalba - "Epidemiologia española," Madrid, 1802, 201, ff. Ant. Mar. Barbosa - "Estudios sobre o garratolli on croup," Lisboa, 1861. Glesias - "Siglo medico," 1862, No.434, ff.). We next find angina maligna in 1596 at Granada, in Estremadura in 1603, in New Castile in 1603, its acme of prevalence not being attained, however, until from 1610 to 1618: the worst year of all seems to have been 1613, the same receiving the designation of "Anno de los garrotillo" in commemoration of its frightful devastation. After a temporary lull, it again comes into prominence amongst the chronicles of 1630, raging with renewed potentiality in Saragossa, and other districts of Arragon (Gil de Pina - "Tratado de la curacion del garrotillo," Zaragoca, 1636. Zacutus Lusitanus - "Prax. med., lib. I, obs.99, op. Lugd., Batav., 1667, III, 23), as well as in Antequera (Gutierrez de Antrade - "Tratado del la enfermedad del garrotillo); in Alaejos in 1645 and 1646 (De Villa Mediana - "Consulta de los carbuncos que cormen la Villa de Alaejos," Valladolid, 1663); in 1666the disease seemed to have diffused itself over the entire country (Vasquez - "Morbi essentia, qui non solum per hanc insignem urbem Toletanam, sed totam Hispaniam sparsim grassatur," Toledo, 1669). No record, however, of the disease having visited Portugal before 1626 exists: during that year its malignancy seems (according to Barbossa (loc. cit,) who quoted from two manuscript records of this epidemic, relating to the town of Olivenza, preserved in the Archives of Lisbon, printed accounts of the epidemic not being extant) to have been but slight.

In Italy, angina maligna appears to have been more or less epidemic in 1610, in Mantua, Lombardy, and

Guastalla especially (Corradi - "Annali delle epidemie occorse in Italia," III, 16. Grassi - "Consultatio - Med. morborum qui et Gustalae et Mantuae nunc vagantur," Mantua, 1610; Ravicio - Influsso maligna osservato nella terra di Guastala l'anno 1610," Venet., 1613); it did not, however, become pandemic until from 1618 to 1642. In 1618 - the same year that such havoc was wrought by it in Spain - the disease broke out in Naples, from thence spreading itself over Sicily and the Papal States (Boncore - "De populari ac pestilenti gutturis, annexarumque partium affactione, nobilissimam urbem Neapolim ac totum fere Regnum vexante.," Neap., 1622. Carnevale - "De epidemico strangulatoria affectu," Neap., 1620. Foglia - "De anginosa passione per inclytam hanc Neapolis civitatem vogante.," Neap., 1620. Nola - De Epid. phegmone anginosa grassante Neapoli.," Venet., 1620. Sgembati - "De pestilenti faucium affectu Neapoli saeviente," Neap., 1620. Corradi, loc. cit., p.26, et seq.); - the latter having a particularly severe outbreak in 1633 and 1634 (Boronius - "De peripneumonia anni Domini, 1633; flammiam infestante libri duo,"Foro Livix, 1636. Cletus - "De morbo strangulatoris opus," Romae, 1636; Corradi, pp. 142, 146). - appearing in Sicily (Cortesi - "Miscellan. med.," Messane, 1625, Dec. IX, 696, 705; Corradi, p.44) in 1623, as well as in Sardinia and Malta; to become pandemic in Sicily in 1632 (Alaymo - "Consultatio pro ulcer syriaci curatione," Panormi, 1632, Corrade, p.138), manifesting itself in San Remo in 1639 (Bacini - "De angina ulcerosa tractatio," Papiae, 1619; Carradi, p. 151), where it continued to prevail until 1642, and at the same time, in a very malignant form, in Naples(Severnis - "De paedangone

maligna," S.l., 1652; "De recondita abscessum natura," Frankf. 1643, p.428, Corradi, p.154).

In the eighteenth century prevailed in various parts of both hemispheres in a very malignant form, but less so than dur ing the preceding century in Spain and Italy. Thus, in the year 1701 an epidemic of malignant sore throat broke out in the Ionian Islands (Tournneford - "Relat. d'un voyage du Levant," Paris, 1717, I, 65), and in various provinces of Spain (Morejon - loc. cit., VI, 349). In 1715 the disease prevailed in Aqinlar de Campos (Fernandez -"Tratado de las epidemies malignas," Madrid, 1725); in 1749, - known as "bolhos de Galicia" (Aloysins Barbosa - "De angina ulcerosa ab anno 1786 ad annum 1787 apud Leiriam epid. Grassante comment.," Lisbon, 1789) - at Lisbon, Leiria, and other towns in Portugal; in New C astile and Galacia(Thiery - "Observ. de phys. et de med.," II, 160) from 1750 - 1762; in Valencia (Pasqual - "Tratado del garrotillo maligno," Valencia, 1784); and once again at Lisbon in 1786 (Barbosa - loc. cit.). About this time severe spidemics of angina maligna seem to have occurred in France, namely at Paris (Chomel - "Diss. sur le mal de gorge gangreneux," Paris, 1769. Malouin - "Hist. de l'Acad. des Sci.," i746, i5i; 1747, 563; i748, 561. Boulland - "Quest. Med.: Am angin. gangraen. emeticum? Paris, 1750). Versailles (Bordeu - "Oeuvres completes; Paris, 1818, II, 776), Orleans (Du Hamel - "Hist. de l'Acad, des Sci.," 1747, 337), Lille - (Boucher - "Jour. de med.,"

VIII, 556), Rouen (Le Cat - "Philos. Trans.," XLIX, pt. I, 49), Amiens (Malouin - loc. cit., 1748), Chalons-sur-Marne (Navier - "Diss. sur plusieurs malad. populaires à Chalons," Paris, 1753), Montpellier (Blorden - loc. cit., I, 80), Nerac Raulin - "Traité des malad. occasionées par les promptes at fréquentes variations de l'air," Paris, 1752, 142), and Bearn (Borden - loc. cit., II, 755). Still further epidemics are reported as having occurred at Paris (Borden - loc. cit.), in 1758, 1759 and 1762; at various Norman towns (Lepecq de la Cloture - "Topogr. der Normandie," 1794, 78, 286) - especially in Lisieux and Forges - in 1774, and, in 1787, at Poitiers (Lamarque - "Jour. de méd.," LXXXIII, 169).

About this time also angina maligna is chronicled as having, for the first time, become epidemic in England and Holland, and, for the second time, in Italy - about Cremona (Ghisi - "Istoria delle angine epid. in Ponte Longo," Cremona, 1749) in 1747, reaching Istria (Panzoni - "Beschreibung der Krankh., Welche 1786 in Istrien geherrscht haben," 1801, 18, 102) in 1786. The disease appears to have reached Holland in 1745 or 1746 being first observed at Dalhem, in the vicinity of Liege (Zaff - "Synopsis observ. medic.," Lugd., Batav., 1751), reaching Utrecht (Keetel - "De angina epid. annor. 1769 et 1770," Utrecht, 1773), in 1750, - being likewise prevalent there from 1769 to 1770, - and Dordrecht

and Rotterdam (Stocke - cited by Israels, loc. cit., 19) in 1754. The disease appeared - simultaneously with the Dalhem epidemic - in Cornwall (Starr - "Philosoph. Trans.," XLVI, 435), commencing at Liskeard, where it remained epidemic until 1748. Many cases were reported in London (Simmons - "Medical Facts and Observations," 1790, p. 302) in 1790, and from the Chesham district of Buckinghamshire in 1793 (Ramsay - "Transactions of a Society for the Improvement of Medical and Surgical Knowledge," II, 25).

Not until the middle of the eighteenth century was the disease known to have been epidemic in Switzerland, Germany and Sweden: in the first mentioned country it is reported as having been especially destructive of human life in Simmenthal (Langham - "Acta Helveticorum," II, 260; "Beschreibung Verchied. Merkwürdigkeiten des Simmenthales," Zürich, 1753) in 1752; and in that year also in the Hartz district of Germany (Herzog - "Diss de febre catarrh maligna epid. angina gangraenosa stipata," Hal., 1788); in Rampitz (Bergen - "Nova acta acad. Leopold.," 1757, Obs. 83, I, 336) in 1755, in 1790 at Osnabrück. From 1755-1762 a severe epidemic prevailed in Stockholm, Upsala, Colmar, and various parts of Sweden (Berg - "Forsök till de i Sverige gangbare sjukdomar för aret 1755," p.36; Wilcke - "Diss. de angina infantum," Upsala, 1764 - in Sandifort's "Thesaurus dissertationem," II, 347; Rosen v. Rosenstein - "Kenntnaiss und Kur der Kinderkr.,"

Gött., 1781, p. 622; Wahlbom - "Berättelse till Kongl. Colleg. med. for aret 1762," p.181).

About this time also angina maligna is first reported as having been epidemic in America. Thus, the disease was productive of great mortality in New York in 1752 (Middleton - "Cases of angina trachealis," New York, 1781), 1771, and 1772 (Bard - "Trans. of the Amer. Philosoph. Soc.," I, 396), in 1799 becoming wide-spread over the Northern States, Virginia especially, the fact being emphasized by the death of Washington from it, at Mount Vernon, near Alexandria, in that year (Cullen - "First Lines of the Practice of Physic;" Phila., I, 260). Both Moseley ("Treatise on Tropical Diseases," London, 1787) and Lempriere (Pract. Observ. on Diseases of the Army in Jamaica," London, 1799, I, 46) report the disease as having been epidemic in Jamaica about this time.

Except, perhaps, in France a marked remission in the epidemic prevalence of diphtheria seemed to have occurred almost everywhere from the end of the eighteenth century until about the year 1860: epidemics of other diseases now became vastly more troublesome. In France alone does the disease seem to have been epidemic at this period. The writers of that time certainly make no mention of its occurrence elsewhere. In the year 1860, however, the disease became pandemic, and it has continued without marked general remission to prevail ever since.

During the first half or so of the nineteenth

century (1800 to 1843) Southern Europe appears only occasionally to have been visited by diphtheria, e.g., Padua (Penada - "Observ. med. - meteorol. di Padova," Quinq. IV, 286, 304) in 1805; Crete (Sieber - "Reise nach der Insel Kreta im Jahre, 1817," Luz., 1823) in 1816; and Lisbon in 1835. France seems particularly to have been afflicted for the deaths recorded there from 1810 to 1811 - at Lyons especially - were numerous (Martin in Ozanam, I, 241). Then comes the account which Bretonneau gave in his celebrated work of the epidemic which he studied in Tours from 1818 to 1821, following which we have recorded epidemics in Paris (Ribes - "Rev. méd.," 1828, Oct., 1843), in the Lot (Desgenettes - "Bull. de la faculté de méd. de Paris," 1819, VI, 395), in Nantes (Prion - "Journ. gén. de méd.," XCVI, 360), in Arras (Ref. in "Arch. gén. de méd.," VII, 463), and the Eure-Loire district (Gironard - "Jour. gén. de méd.," CIII, 312). The disease, however, did not attain its acme of prevalence in France until from 1825 to 1836, during which period many severe epidemics were recorded, e.g. - in the Orléannais (Bouillon - Lagrange - "Gaz. hebd. de méd.," 1859, Juin, 359), especially in Loiret (Ref. in "Revue méd.," 1829, Oct., 137); in Touraine (Menon - ibid., Aug., 262; Bretonneau), chiefly in Loire-Cher (Gendron - "Jour. gén. de méd.," CIX, 32; "Arch. gén. de méd.," 1883, Nov., "Jour. complém. du Dict. des sci. méd.," XXIII, 346; "Trans. méd.," III, 293. Ranque - "Annal. de méd. qhysiol.," 1828, Fevr.), and Indre-Loire (Guimier - "Jour. gén. de méd.," CIV,

165. Ref. in "Rev. méd.," 1829, loc. cit.. Bridel - "Jour. de méd. et de Chir.," 1835, Mars); in Anjou - Maine - Loire (Ouvrard - "Rev. méd.," 1826, Dec., 512. Ridard - "Gaz. méd. de Paris," 1834, 273), Sarthe (Lespine - "Arch. gén. de méd.," 1830, Aug., 519), and Mayenne (Lemercier - "Bull. gén. de thérap.," 1833, Nov.); in Brittany - Nantes (Prion - loc. cit.); in Normandy - Orne (Bianquin at Martin - cited by Emangard, "Mém. sur l'angine épid.," Paris, 1829); in Picardy (Bouillon - Lagrange - loc. cit.) - Seine-Marne (Ferrand - "Diss. sur l'angine membraneuse," Paris, 1827) and Seine (Bourgeois - "Rév. méd.," 1829, I, 159, 323; Jour. gén. de méd.," CVI, 122, 436, CIX, 137); and in the Isle-de-France. Outside of this north-west region diphtheria was only observed to be epidemic once during the period referred to, namely at Limousin in the Haute-Vienne (Mazard - "Bull. des sci. méd.,LX, 138). After this, however, epidemics of the disease were recorded at Paris (Boudet - "Arch. gén. de med.," 1842, Fevr., Avril; Becquerel - "Gaz. méd. de Paris," 1843, No. 43 ff.) in the Nièvre Department of Nivernais, Saône - Loire district of Burgundy (Bouillon-Lagrange - loc. cit.), and, in the East of France in 1841.

About this time diphtheria seems to have been attended by a high mortality in Switzerland, especially at Geneva and various parts of the Canton Vaud (Baud - "Bibl. universelle," 1829, 233, 333). In Germany too, there were epidemics reported from Marienwerden (Maercker - in Hufelands "Jour. der

pract. Heilk.," 1804, XIX, Heft. 3,78) in 1801, and many places in East Prussia (Elsner - "Bericht. über den Gesund. Ostpreuss. in Jahre, 1801," Königsb., 1802). Later, the disease has been described as epidemic at Brotterode, -Harz,- in 1837 (Fuchs - "Kurhess. Zeit. f. Heilk.," 1845, II, Heft.I, 13), and at Luneberg in 1841 (Hannov. Annal. der Heilk.," 1842, N.F., II, 410) from which latter place it was said to have been absent for nearly thirty years.

In the early part of the nineteenth century the disease appears to have been fairly common in these islands, more especially at Dublin (Cheyne - "The Pathology of the Membrane of the Larynx," Edin., 1809; Bewley - "Dublin Jour. of Med. Sci.," 1836, Jan., 401) Glasgow (Perry - "Glasg. Med. Jour.," 1881, July 2), Edinburgh (Abercrombie - "Diseases of the Stomach and Intestinal Canal," Edin., 1828; Begbie - "Edin. Med. Jour.," 1862, May, 995); afterwards, in 1817, at t Kent ("Second Report of the Medical Officer of the Privy Council," 1859, London, 460, 244), in 1819 and 1825, at Glasgow (Brown - Glasg. Med. Jour.," 1881, July 3; Mackenzie - "Edin. Med. Jour.," 1825, April, 294; "Med. Chir. Rev.," 1827, Jan., 290) and, in 1825, at Kelso (Robertson - "Edin. Med. and Surg. Jour.," 1826, Apr. 279).

Simultaneously with the above we have recorded an epidemic of diphtheria at Skien in Norway (Munck - "Eyr," 1826, I, 222), and during various periods from the United States of America - Philadelphia in 1809 (Caldwell - loc. cit.), New York (Belden - "Amer. Med.

Rec.," 1828, Jan., XIII, 123), Salem in New Jersey (Beesley - "North Amer. Med. and Surg. Jour.," 1829, Jan., p. 66), Damville in Kentucky (Smith - ibid.,1829, Oct., p. 253), Northumberland,Pa., in 1830 (Jackson - "Med. Times and Gazette.," 1859, April, p. 457), and in Orizaba, in Mexico, in 1836 (Poncet - Mém. de méd. milit.," 1863, Févr., p. 90).

For twenty years subsequent to the period above described diphtheria seems to have manifested itself in various parts of the globe, but only either in the sporadic form or as strictly localised minor epidemics; but this, however, with the notable exceptions of France, Denmark, and Norway where it seemed, commencing with 1844, to have become widespread. During the same years the disease was reported as having been epidemic in the Italian Peninsula, viz., in 1844 and 1845 in Vasto (Barbarotto - "Filiatre Sebezio," 1846, Maggio), Castelpetrosa (Ferrara - ibid., 1845. Feb.), and other localities of the Abruzzi, Molise, and the Kingdom of Naples (Guaita - "Lo Sperimentate," 1886, No. 18), and in 1854 at Fonzaso in the province of Belluno (Facen - "Gaz. med. Lombard," 1866, No. 18). From 1844 to 1853 numerous cases were reported in Germany: in various parts of the Grand Duchy of Nassau (Santlus - "Jour. f. Kinderh.," 1854, Heft. 7, 8; and "Med. Jahrb. f. das Herzozth. Nassau," 1864, Heft. 21, p. 146), Griefswald (Stubenrauch - "Die angina membran. epid.," Grypt., 1845) in 1844-1845, and at Königsberg (Bohn - "Königsb. Med. Jahrb,." 1858, I, 110) from 1850 to 1851. Prior to the great epidemic commencing in 1857 in England, many sporadic cases of diphtheria were observed from 1844 to 1855;

in London, Kent, Lincolnshire, Herfordshire, Staffordshire, Norfolk, Devon and Cornwell ("Second Report of the Medical Officer of the Privy Council," p. 174; "Journal of Public Health," 1855, Dec., p. 361; 1856, Oct., p. 302; 1857, April, p. 89; Radcliffe - "Trans. Epidem. Soc.," 1863, I, 328); but during that time the disease appeared to have been epidemic in two places only, namely in Haverfordwest (Wales) in 1849, (Bronn-"Med. Times and Gaz.," 22, 670); and Launceston in 1855, (Thomson- "Brit. Med. Jour;"1858, June, p. 440) So too, in Sweden, both North and South there were many cases of angina maligna observed from 1852 to1855, ("Sundhed Berättelse", 1852, p. 30; 1853, p. 68; 1855, p. 40; Wistrand -"Ofversigt over Kgl. Veteusk. Akad. Förhand;"1856, p. 265; 1857, p. 423) as well as in Amsterdam and various parts of Holland from 1854 to 1857, (Van Cappelle - "Nederl. Tydschr. Voor. Geneesk", 1862, 3, 506) Belgium, and Switzerland, in which latter country it was reported as being particularly virulent in the canton of Zürich, (Wäckerling - "Scheweiz. Zeit. f. Medicin," 1856, p. 164).

Diphtheria seemed in France to have confined itself chiefly to the north and east during the period under discussion. It was, for example, observed in Paris in 1846 to 1848 (Vanthier - "Arch. gén. de méd," 1848; Mai, Juin; Empis - itid,1850, Févr, Mars) at L'aigle in Normandy (Mayier - "Gaz. méd de Paris," 1853, p. 585) in 1850, in Vitry - le - Francois, Epernay, etc. in the Department Marne, Champagne (Valetia - "L'Union méd," 1855, No. 105;) Gaultier de Claubry -

"Mem. de l'Acad. de Med," 18, 63), at St. Pol, Department Pas - de - Calais (Ibid), in 1852, in the Arrondissement of Aisne, Dep. Aisne (Ibid; 19, 41), and in Valenciennes, Dep. Nord (Idem), in 1853, and in Paris Boulogne, and elsewhere, in 1855 (Proussean - "Gaz. des Hôp." 1855, ~~Juill~~; No. 86; Oulmont - "Rev. méd. - chir," 1855, Juill; Isambert - "Arch. gén. de méd." 1857, Mars, 325; Avril, 432; Gubler - ibid; 1857, Mai; Fieve, "Gaz. des Hôp," 1856, No. 8). From the South of France on the other hand one hears of an epidemic only in 1852 in the Arrondissement of Marmaude, and of another in 1853 at Avignon (Gaultier de Claubry - loc. cit.). The epidemic of Angina Maligna which occurred among the French troops in 1854 and 1855, during the war in the Crimea and in Turkey (Haspel - "Gaz. méd. de Paris," 1855) seems in all probability to have been connected with the prevalence of the disease during that period in France; when moreover the malady became more or less generalized in Denmark, groups of cases beginning to show themselves in increasing numbers from 1844 to 1846 on the island of Fuhnen and in Amt Viborg in Jutland), In the winter of 1847 - 48 an epidemic of Angina sprang up at Logstor (Amt Aalborg, Jutland); in 1847 the disease was epidemic also in Odensee and Vissenbjerg (Fühnen), and at several places in Jutland; and in the following years at many parts of Seeland as well as throughout the Danish Islands generally(Beck - Bibl. for Laeger," 1849, Apr. 257, and "Sundhedskoll. Forhandl," for 1848, 33; 1849, 29; 1850, 23; 1851,20;

1852, 38; 1853, 68; 1854, 23). In Norway the disease began to be prevalent about the same time: first in 1845 at Trondjem (Roll - "Norsk. Mag. for Laegevindensk," 1848, 2, 1); in 1845 at Thoten (Raabe - ibid, 78), in 1847 at Lavanger and Skogn (Dietrichson - ibid, 73); in 1855 the disease became prevalent throughout the entire country (Cold - "Ugeskrift for Laeger 1867", No. 28), after a brief localisation at Namdal (Jebe - ibid, 393), During the same years the disease was frequently observed in North America, namely, at Salem(New Jersey), in 1844 (Gibbon - Amer. Jour. of med. sci," 1845, July, 80), Philadelphia in 1845 and 1848 (Meigs- ibid, 1847, April, p. 277; 1849, April, p. 307), and in Morgan, Monroe and Guernsey (Ohio) from 1847 to 1849 (Welsh - "Ohio Med. and Surg. Journ." 1850, May).

Coming now to the period commencing with 1860, diphtheria may be regarded as practically universal, forthwith France especially came to be the centre of a great pandemic; next to it in the order of invasion came the Iberian Peninsula, Holland and England; then Germany, Russia and North America, a little later, Scandanavia; and, lastly, the Italian Peninsula and the South - east of Europe.

Beginning with the close of the year 1859, France everywhere became visited by diphtheria(Bouillon - Lagrange - Gaz. hebd. de Med, 1859, Juin, 359; Bouardel - ibid, 1869, Nos. 3 and 41), where its manifestations were of an extremely malignant character; and it was now no longer confined as formerly to the northern and

eastern provinces (Brittany, Normandy, Picardy, Ile - de France, Champagne, Lorraine, Poitou, Sologne, and the Orleannais, for it broke out in the southern and western regions also) namely, in Burgundy (Simyan - "Gaz. des Hôp. " 1854, 334), Auvergne(Pitavy - "Etude sur une épidem. de diphthérie," Paris, 1878), Lyonnais (Fonteret - "Lyon méd," 1868), Provence, Languedoc (Courty - "Recherches sur les conditions météorotogique de développment du croup et de la diphtherie, "Montpellier, 1862 Gingibre - "Montpellier médical," 1866, Juin, 526), Guyenne (Silva - "Clinique Européene", 1859, No. 39; Marmisse - "Jour. de méd. de Bourdeaux," 1868, Mars, 127), and Saint Onge (Robert - "Observ. d'une Epidém. de croup," Paris, 1859; Borsaton - "L'Union med.", 1869, Mars, 23). In many of these places the disease seemed now to have appeared for the first time; thus according to Bouillon - Lagrange, (loc. cit.) there had been no diphtheria in the Southern part of the Dep. Seine - Oise before 1857; Bodélio (Compt. rendu des épidémies de Morbihan en 1865," Vaunes, 1866, 17) Vouches for the same at Morbihan. according to Pitavy, the disease became prevalent for the first time in 1859 in Puy - de Dôme, Auvergne; Courty in 1862 said the same with regard to Montpellier; in Lyons down to 1865 (Fonteret - loc. cit;Marmy et Quesnoy - "Topog. et Statist. méd. du département du Rhone." Lyon, 1866, 547), it had only been seen in sporadic cases , but became wide - spread from that date; in St. Die,

(Vosges), it became epidemic for the first time in 1880 (Ende - "Mém. de méd. milit," 1882, Juill, 352).

The disease shewed itself in the Iberian Peninsula first in isolated cases at Lisbon in 1857 and 1858; but it was not until 1859 that it assumed the proportions of an actual epidemic, spreading gradually over a large part of the country (Barbosa - "Jour. da sociad. das sci. med, de Lisboa, " 1868; Beer - "Deutsch. Klinik," 1870; No. 34) so much so indeed that Ferraira de Macado Pinto (Medicina administrava," Coimbra, 1863, 3, 304) described it among the endemic maladies of Portugal. In Spain, on the other hand the disease began to spread in 1859 also, until it covered the whole country (Rendu - "Gaz. des Hôp.,"1884, No. 107, 849), reports, however being forthcoming chiefly from Segovia in 1861 -63. (Aravaca y Torrente - "Sigle med., "1864, Julio) and from Huelva (Ullersperger -"Monat. f. Med. Statist." 1875, Nos. 2 and 9) in 1874. the disease made its appearance in Holland first in 1857 being especially prevalent at Amsterdam; it reappeared there in 1858 as an epidemic and afterwards broke out in the provinces of Groningen, Geldern and Friesland; about the same time on the island of Overflakke and at other points of the province of South Holland, thus gradually overrunning the whole Kingdom. The Mortality, however, was not great: in1859 - 1863, among a population averaging 3,000,000, there were only 1973 deaths reported, or about 400 per annum; in 1866 - 1870, they numbered 2914, or a yearly average of 600, the provinces that suffered

most being Gelderland, Seeland, Utrecht, Groningen, Drenthe, and North Holland. In 1871 the epidemic seems to have subsided considerably , to become as good as extinct in 1875 or the year following (Hart - On Diphtheria and its History, Progress, Symptoms, etc." London, 1859; Grenhow - "On Diphtheria," London,1860; Report in "Trans. Epidem. Soc.; 1860 - 63, 1, 35; Radcliffe - ibid., p. 328, and 2, 197; Bryden -"Brit. Med. Jour.," 1857, Nov., p. 967; Camps - ibid., 1858, March. p. 283; Pridham - ibid., April, p. 305; Atcherley ibid., June, 495; Stiles - ibid., July, p. 628; Pound - ibid., Sept., p. 750; Ellis - ibid., 1859, May, p. 420; Rigden - ibid. and 1869, April, p. 348; Cross - ibid., 1859, July, p. 561; Bottomley - ibid.; Jennings - ibid., p. 562; Smith - ibid., p. 566; ref., ibid., Aug., p. 193; Praugley - ibid., 1875, Jan. p. 40; Blyth - ibid., Sept., p. 317; Semple - ibid., Nov., p. 613; McKinder - "Med. Times and Gazette," 1859, Jan., p. 32; Moncton - ibid., p. 93; Feb., p. 222; Hillier - ibid., Jan., p. 107; Sandefson - ibid., May, p. 373; Ballard - ibid., July, pp. 53, 77; Bridger - ibid., 1864, Aug., Mc. Donald - "Lancet", 1859 Aug., p. 183; Crighton - "Edin. Med. Jour." 1860, Feb., p. 146; Donnes - "Report on an outbreak of Diphtheria at Oaksey," 1883).

Crossing from Boulogne, diphtheria appeared in England in 1857, the first cases being observed in Kent Essex, Surrey, Sussex, Hampshire, Devon and Cornwall, from which it soon diffused itself over the whole of England., and continued to do so - with a slight remis-

sion in 1860 - until the latter part of the year 1863. So far as the epidemic prevalence of diphtheria in Scotland is concerned the accounts are somewhat vague and misleading; but if Begbie's statements are to be credited the disease appears to have prevailed sporadically in Edinburgh from 1858 to 1860, much more conspicuously in 1862, and quite epidemic in 1863 (Christison - "Edin. med. Jour., " 1863, Nov., p. 436); Kincardinshire received a visitation in 1859 (Forman - ibid., 1860, June, p. 114) and Falkirk in 1862 (Hamilton ibid., 1863, Aug., p. 132; Oct., p. 312). From a total mortality from diphtheria, in Scotland, of 151 in 1861, the same increased to 285 in 1862, and in 1863 to 478 - 1 7 per cent. of the mortality from all diseases. Leith suffered most severely, Aberdeen and Edinburfgh next (Radcliffe - "Trans. Epidem. Soc.," 2, 198). Subsequent to this, however, epidemics of diphtheria seem to have been restricted to Letham, (Smith - "Edin. Med. Jour., " 1864, 799), in 1864, Edinburgh (Ref. ibid., 1871, Sept., 287), in 1871, and Auchtergaven, Perthshire (Jeats - ibid., 1876, July 33), in 1875. During this period the first account of diphtheria dates from 1856, in which year the malady showed itself simultaneously at a number of places far apart, namely, at Königsberg, where we have already noted its prevalence from 1850 to 1851 (Bohn - "Königsb. med. Jahrb., 1, 110; Olshausen - De laryngitidis membran. epidem, " Regiom., 1857), in many places in Holstein (Volquartz - "Einige Worte über die Ausschwitz. Bräune," Altona, 1862; Krosz - "Viertlj

f. gerichte. Med., "1884, Jan., 89), and in Munich. and district (Hauner - "Jahr. f. Kinderh.," 1858, 2, 51), where, however, its mortality was slight. During the next five years the disease was observed chiefly in the Southern and western parts of Germany, such as Middle Franconia (Majer - "Bayer. ärztl. Intellig.," 1858, 2, 51) in Bavaria , Würzburg, (Hoffman - ibid., 1881, 325), Munich (Rauke - "Jahr. f. Kinderh.," 1869, N.F. 2, 41),
Rottweil (Rapp - "Würtemb. med. Corresp.," 1860, No.18) in Würtemberg, the Canton of Saar - Union (Ref. in "Rec des trav. du conseil department d'hyg. publ. du Bas-Rhin. de 1858 cis 1859, "Strassb., (865, 52) in Alsace and Nassau (Menges - "Nass. med. Jahrb.," 1863, Heft. 19, 20, 412); but it seems to have occurred also in Thuringia, near Jena (Müller - "Jen. Zeit. f. Med.," 1864, 117), in East Frisea (Kohnemann - "Ueber Diphtheritis, deren Gesch., "Hannover, (1862; Uhlenberg - "Deut Klin.,"1863, No. 50), at Bremen (Lorent - "Jahr. über des Gesundh. in Bremen in den Jahren 1877 - 78,"Bremen, 1880, 32), and in Holstein near Kiel (Bartels - "Arch. f. klin. Med., " 1867, 2, 367). Connected with these scattered foci of the disease (which have subsequently become for the most part permanent seats of diphtheria) comes the general diffusion of it over nearly the whole of Germany in the year following. In 1862 and 1863 malignant sore throat was already epidemic at many places on the Baltic, such as Danzig, Griefswald (Zielke -

"Virchow's Arch., " 1868, 40, 428) and Rostock (Classen ibid., 1871, 53, 260); also in the Duchies (Curtze - "Zeit. f. Med. chir. und Gebursh.," 1866, N.F. 5. 259), in the Kingdom of Saxony (Förster - "Prager Viertl. f. Heilk.," 1864, 81; Geissler - "Die Ausbreitung der Diphtherie im Königreich. Sachsen," Leipz., 1880; Spengler - "Arch. f. klin. Med.," 1883, 34, 293), in Thuringia (Rohde - " Deut Klin.," 1865, No. 1; Kunze - "Berl. klin. Woch.," 1866, 477), and in many parts of Bavaria (Seitz - Diphtheria und Croup.," Berlin, 1877, 195). The disease, however, became still more diffused in the following years; down to 1881 it has been reported as epidemic in Holstein (Bartels - loc. cit.; Bockendahl - "Sanitat. über die Provinz Schleswig Holstein f. das Jahr. 1872,und ff."; Krasz - loc. cit.), Hamburg (Medicinalb. uber die Med. Statistik des Hamburger Staates"), Berlin and neighbourhood, Hanover (Schuchardt - "Hannov. Zeit. f. Heilk.," 1866, 1, 521, 1867, 293; Reinecke - "Die Diphtheritis in Göttingen, "Gött., 1884, Diss.), Thuringia (Maulhardt- "Berlin klin. Woch.," 1866, 498; Claes - "Die Diphtherie in Mühlhausen in Thüringen,"Diss., Mühlh., 1870; Pfeiffer- "Beitz. zur med. Topogr. in Thüringen," Jena, 1873, 100), the Rhine districts (Ueber - "Corresp. f. die Mittelr Aerzte," 1868, 2, 1233; Hansgen - "Deut. med. Woch," 1876, No 3 et segr.; Eschbaum - "Beitr. zur Statistik einger ~~a~~acut - entzündl. und Infections." Bonn, 1880, p. 37), Hesse (Grau - "Jour. f. Kinderkr.," 1868, 1, 149), Frankfort - on - the - Main ("Jahresb.

über des Medicin. der Stadt Frankfurt a. M. f. das Jahr 1868," p. 68; König - "Berl. klin. Woch," 1876, p. 198) Würtenberg (Ref. in Würtemb. med. Corresp.," 1865, p. 182, 1867, p. 38, 185, 1869, p. 350; Ehrle - "Pathol. der epid. Diphtheritis," Tubingen, 1867), and Bavaria (Seitz - loc - cit., p. 199). In Switzerland, however, diphtheria seems to have obtained a poor hold According to Demme ("Jahr. f. Kinderh.," 1868, 1, 2) a small epidemic occured during the winter 1866 - 67, in the Childrens Hospital at Bern, but no case of diphtheria was observed outside of it.

It was not until after the period under discussion that diphtheria established itself to any marked degree in the Austrio - Hungarian Empire, Besides a notice of an epidemic in the district of Wippach (Schwegel - "Sanität. vom Herzogth. Krain f. 1861 - 62." Laibach, p. 33). Carniola, during 1859, 1861, and 1862, the earliest account of its epidemic prevalence dates from 1870 in which year the disease appeared in the South - eastern frontier districts of Transylvania (Gusbeth - "Zur Geschichte der Sanität. in Kronstadt," (Kronst., 1884, p. 59), having been introduced from Roumania it spread by degrees, but so slowly that it did not reach Hermannstadt (Binder - "Wien. med. Woch.," 1873, No. 33) until 1872. In 1874 an epidemic occurred at Bukowina, Czernowitz (Lazarús - "Wien. med. Presse," 1875, Nos. 38,39), and in Hungary ("Statist Jahrb. f. Ungarn," 1874); and in 1875 the disease became epidemic for the first time in Vienna (Stentzel - "Wien. med. Zeitung." 1879, Nos. 14 - 19; Herz - "Jahr. f. Kinderh.," 1885, 22, 311).

In the Russian Empire, many cases were observed at Moscow as early as 1853; but the first accounts of epidemicsin that country date from 1858 and 1859, in which years diphtheria was widely diffused (Ref. in "Med. Ztg Russe.," 1860, p. 97) appearing at a number of places in the Government of St. Petersburg (Norden - ibid., 1860, pp. 49, 57), at Moscow (Kronenberg - "Jour. f. Kinderkrank.," 1861, 36, 93; Blumenthal - Jahr. f. Kinderheilk.," 5, 9), and in the Government of Orel (Maydell - "Med. Ztg. Russl.," 1860, p. 97). In the southern provinces of the Empire, it occurred first in 1869 at Balta, Podolia (Jordanoff - "Considér. et observ. sur l'angina diphthéritique," These, Paris, 1867) And from 1872 to 1879 it spread with terrible destructiveness over a great part of Southern Russia (Ucke - "Viertelj. f. gerichtl. Med.," 1881, Jan., p. 158; Kupffer - "Petersb. med. Woch.," 1882, Nos, 19, 20), the sick being numbered in every village by the hundred and in every commune by the thousand, no child attacked ever recovering. The disease was supposed to have been introduced into Southern Russia from Roumania, where it had shown itself for the first time in 1868 as a malady hitherto unknown, and had continued to spread without interruption until a date subsequent to 1874 (Felix - "Wien. med. Woch.," 1870, No. 36; Kalewitch - "Consider sur l'Epidémic d'angine diphtheretique de Bukarest," Paris, 1871, Klein - "Memorabilien," 1874, No. 9).

During this period also are accounts of epidemics in Denmark ("Sundhedsc. Aarsberetn.," loc. cit., and ref.

in "Jour. f. Kinderkr.," 1869, 38, 89,95), from 1861 to 1866, from 1861 to 1875 in Sweden ("Sverges Sundheds-col. Berättelse", ar 1861 - 74), and from 1860 to 1868 in Norway (Greve - "Norsk Mag. for Laegevidensk," 1862, 16, 625; Thorsen. - ibid., 1865, 19, 279; ref. in "Monat. f. med. Statisk.," 1874, 80, Kjerulf). From 1863 to 1870 the cases reported numbered 18,156, of which 4176 were fatal; in Norway from 1866 to 1870 there were 9122 cases and 1649 deaths, In Iceland diphtheria became prevalent for the first time in 1856; it started from Reykjavik and spread in the following years over the whole country (Hjaltein - "Edin. Med. Jour., " May, 1866). It reappeared there in 1860, having been introduced from the Faröe Islands where it was then prevalent ("Sundhed. Aarsb.," 1861, 370); and that epidemic was not stamped out until 1864 (Finsen - "Jagltag. angaande Sygdom. i. Island.," Kjöbenh.," 1874, 37).

About this time Italy is reported as being again visited by diphtheria (Parola - "Geographia nosologica dell' Italia," Torino, 1881, 493 and Guaita - "Lo Sperimentale," 1882, Maggio, 449), which appeared first at Florence in 1861; spread in the following year over the greater part of Tuscany, and continued to be epidemic for more than ten years (Morelle e Nesti - "Istoria clin delle difterite osservata nella città di Firenze e suoi contorni del 1862 al 1872," Firenze, 1813; Mancini - "Raceog. med.," 1873, No. 25; Pierazzini - "Annal univ. di med.," 1880, 254, 464) with varying range and intensity, the epidemic of 1871 being an especially Malignant one. At the same time as the general outbreak in Tuscany

it appeared in Venetia whence it was reported as being prevalent, down into the seventies, at Udine, Belluno, Verona, Vicenza and other places (Tamburlini - "Gas. med. Lombard.,"1873, 231; de Sabbata - "Osservaz. della difteria," "Udine 1879, Facen - loc. cit.,Bubola- "Gaz. med Veneta," 1864; Donati - "Annal. univ. di med." 1874, Gennaio, 3, Agostini. - loc. cit.) From 1871 the disease overran the greater part of Lombardy (Commissionsb. in "Annal. univ. di med.," 1874, Settemb. 647; Calimani - "Gaz. med. Lombardy" 1875, 409; Dell'Acqua - ibid., 1876 301, Mascherpe - ibid., 301 Casali - ibid., 441); and in the years following it became wide - spread in the Emilia, Rome (Aitkin - "B. M. Jour.," 1873,March 341), Umbria, the Marches,nNeapolitan territory (Menzies - "Edin. Med. Jour., "1872, Sept, 217; ref. in "Gaz. med. Lombard.," 1876, 402). and in Sicily (Parola - loc. cit.) so that according to Parola,Piedmont was the only part of Italy that enjoyed something approaching immunity. Corresponding to the period of its prevalence in Italy is the epidemic outbreak of diphtheria in Malta (Gulia - "Notizie clin, sulla difteria," Malta, 1870). In Greece it had already made an appearance - its first - in 1865, in the Epharchy of Phthiotis (Hellas), where it continued thereafter to be endemic (Rizopulos - "Congrès. des méd, Grecs à Athenes in 1882", Constantinople, 1883, 17; Valssopulos - ibid. 22). In many parts of Turkey also it was reported as prevalent in 1868 - 71 (Marroin - "Arch. de méd. nav., 1869, Oct., 308, Dec., 461; Mauricos - ibid,, 1876, 10)

In North America just as in Europe, diphtheria has come to be more or less epidemic since 1856, the first

cases being reported from California (Gibbons - "Annual Address before the Francisco Medical Society," 1857 Fourgeand - "Diphtheritis, a concise history and critical Essay," Sacramento, 1858, Whitney - "Trans. of the Californian State Med. Soc., 1858, Bleke - "Pacific Med. and Surg. Jour.," 1858, Aug., Logan - "Dobells Reports," 1871, 2) and the State of New York (Willard - Trans. of the New York State Med. Soc.," 1858, Chapman - "Boston Med. and Surg. Jour.," 1863, Feb., Jacobi - "Jour. f. Kinderkr., 1861, 36, 153, and "Treatise on Diphtheria " New York, 1880; Bowditch - "Trans. of the Amer. Med. Assoc., " 1878, 29, 585; "Second Annual Report of the State Board of Health New York," 1882, 4). Soon after this it appeared in the New England States - Connecticut (Beandley - "Boston Med. and Surg. Jour.," 1859, 87, 439; Matthewson - "Communications of the Connecticut State Med. Soc.," 1865, 132), Providence, Massachusetts, Vermont (Ref. in "Lancet", 1863, 1, 222; Stevens - "Trans. of the Vermont State Med. Soc.," 1865 and Rhode Island (Parsons - "Trans, of the Amer. Med., Assoc.," 1865, 132); in Peunsylvania, - Particularly Philadelphia (Jewell - "Amer. Jour. of Med. Sci.," 1860 April, 390; Keller - ibid. July, 125; Read - ibid., Jan 1861, 138; Jewell - ibid., July 76 and July 1864, 107; "Trans. of the Penn refs. in "Trans. of the Pennsylvania State. Med. Soc.," 1862 - 77). New Jersey (Ryerson - "Trans. of the New Jersey State Med. Soc.," 1859, 5, and 1861, 27), and Virginia (Le Cato - "Awer. Jour. Med.

Sci. ," uly, 1865, 44); then in Indiana (Brower - "Trans. of the Indiana State Med. Soc.," 1860 and Illinois ("Rep. of the Board of Health of the city of Chicago," 1871), Mississipi (Williamson - "Amer. Jour. of Med Sci.," July, 1860, 99; Goldsmith - ibid., April, 1861, 392) and Louisiana - New Orleans (Chaillé - "New Orleans Med. Jour," July, 1870, 576); and, lastly, in the north - western territories, Kansas (Brock - "Trans. of the Kansas State Med. Soc., 1867), and Oregan (Gisan "Amer. Jour. of Med. Sci.," Jan., 1865, 78). In North America, however diphtheria has been by no means confined to the United States: it broke out in Nova ScotiA (Dupont - "Notes et observ. Méd. Sur la côte orientale d'Amérique," Montpellier, 1868, 79) in 1861, in Newfoundland (Anderson - "Dobells Reports," 1870, 365) and Prince Edward's Island (Hobkerd - ibid., 414) in 1867; and since 1864 it has been observed in Mexico (Coindet - "Gaz. hebd.," 1864, 376), and was especially destructive in Vera Cruz ("Virchow's Arch.," 1873, 58, 177).

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Leaving the history of diphtheria as we have described it in Europe and America, the importance of the subject demands that some mention be made of the malady in other parts of the world:- Many reports are extant of the disease in the west Indies:- at Havana (Grande - Boulogne - "Rev. de Thérap." Févr., 1860) in 1850 and 1853, on St Thomas (Sundhed. Aarsb.," for 1858, p. 430; 1859, p. 436). in 1858 and 1859, on Martinique and Gadeloupe (Brassac - "Consid. pathol. sur les pays chauds," Montpellier, 1863, and "Congr. internat. de

med. des Colonies," Amsterdam, 1884, p. 30; Carpentin - "Arch. de méd. nav.," 1873, Dec., p. 433) in 1859 and 1860; and in the Bermudas (Smart - "Trans. Epid. Soc.," 1867, 2, 286; "Statist. Rep. of the British Army," 1864 p. 61) from 1858 to 1862. The disease has been from time to time reported from Guiana, but its date of origin appears to be unknown (Lange - "De la Diphthérie Montpellier, 1869, p. 49. At Buenos Ayres where diphtheria is stated to have been epidemic for the first time in 1814 - 23 (Mantegazza - "Lettre med. sulla America meridionale," Thlano., 1860, 1, 329), it has since 1863 become more or less endemic (Seitz - loc. cit. p. 267). In Peru, where, according to Tschudi ("Pester. med. Woch.," 1846, p. 446, the disease is particularly common on the coast in the forest regions, having been first seen at Lima in 1821 ("Valdes - On Diphtheria, 1827); it attained its acme of diffusion in 1850 and from 1855 to 1859; in the latter period it spread southwards from Piuro to Trujillo and Huaco, reaching Lima again in 1858 (Odriozola - "Amer. Jour. Med. Sci.," Oct., 1858, 520; Smith - "Trans. Epid. Soc. 1863, 1, 365).

So far as Africa is concerned the accounts of diphtheria are as scanty as untrustworthy. In Senegambia and in the West Coast the disease seems to have been observed in the sporadic form only. if at all (Borius - "Arch. de méd. nav.," May, 1882, p. 370). on the other hand, however, diphtheria is common enough in South Africa (Fritsch - "Arch f. Anat. und. Physeol.," 1867,

p. 733), especially in the Orange Free State, and there seems to have been a considerable epidemic of it in Caffraria (Lawson - "Trans. Epid. Soc.," 1869, 3, 141) in 1866. On the East Coast of Africa, the disease is said to have become one of the regular maladies so far back as 1837 (Roquette - "Arch. de med. nav.," 1868, Mars, p. 167), it having been imported from Natal. In Réunion (Pelsner - Monat. der Berl. geogr. Gesellsch.," N.F. 4, 275) it became epidemic in 1879 (Dussac - "Seance publ. de la Soc. de méd. de Toulouse," 1841, p. 70) and has been observed there ever since. In Madagascar, on the other hand (Borchgrevink - "Norsk Mag. for Laegevidensk," 1872, p. 234), and the adjoining island of Nossi - Bé, only sporadic cases have been at rare intervals observed (Deblenne - "Essai de géogr. méd. de l'ile de Nossi - Bé," Paris, 1883, p. 163) The Malady appeared also to have become epidemic in St. Helena (Mc. Ritchie - "Trans. Calcutta Med. Soc.," 1838, 8, app. 29) in 1824, but it has seldom there been observed since. According to Pruner (loc. cit. p. 206) diphtheria is to be reckoned amungst the race diseases of Egypt. In Tunis, however, from 1872 to 1876 it broke out as a wide-spread and malignant epidemic (Ferrini - "Lo Sperimentate," 1874, Luglis, 2, Settbr., 288; "Annali univ., di med." 1875, Maggis, p. 193, ibid., 1877. Marzo, p. 254, and Avrile, p. 323; Funaro - "Storis D'une epidemia di difterite osservanta in susa di Tunisi," Livorno, 1876), and in 1882 it was seen there again among the French soldiers garrisoning

the country, having been introduced from Algiers (Maljean - "Arch de méd. Milit," 1884, No. 5, p. 195, Frio-court - "Arch. de med. náv. "Juill, 1884, p. 16). Among the natives of Kabylia (Algiers), Bazille (Gaz. méd. de l'Algérie, 1868, p. 29) has never seen diphtheria; but against this statement in Gauchers account (Ibid 1869, p. 24) of a severe epidemic in 1865 in the settlement of St. Cloud; and it follows from the fact of the introduction of the malady into Tunis in 1882 that Algiers had been visited by it in that year also.

So far as the prevalence of diphtheria in Asea is concerned, there are few reliable accounts. In Smyrna it became epidemic for the first time in 1865; since that date it has extended widely over Asia Minor and has exerted great virulence since then in various places (Latris - "Congr. de Med. Grec. à Athènes, 1882," Constantinople, 1883, p. 139; Scherzer - "Smyrna,"Wien, 1873, p. 31. The Malady seems however, to have been unknown in Syria prior to 1868 (Post - "New York Med. Rec," June, 1868, p. 149), and in Fars, in Persia, before the year 1874 when it continued to be widespread and extremely malignant down to 1878(Tholozan - "Gaz. hebd. de méd., 1878, pp. 491,520). As early as the beginning of the nineteenth century the disease was observed to be epidemic in India., Mc. Gregor ("Edin. Med. Jour.," July, 1805, p. 282) having studied it in Bombay in 1800; and Jackson ("Trans. Epid. Soc.," 1860, 1, 65), in 1833, at Calcutta, where also it seemed to

be very common in 1836. Since then we have evidence of the prevalence of the disease in various parts of the Himalayas not even escaping as witness the fact of an epidemic, in 1856, in a village on their Slopes 6450 feet above the sea level (Francis - "Ind. Annals of Med. Sci.," Nov., 1860, p. 9): Numerous cases were also reported from the hills of Madras, notably from Fort George in 1863 (Chipperfield - "Madras Quart. Jour. of Med. Sci.," April, 1863, p. 427).

From the Malay Archipelago are accounts of an epidemic in Sourabaya and Batavia in 1881 (Schneider - "Geneesk. Tijdschr. voor Nederl. Indie." 1881, 10, Affl. 2, p. 129; 5, d. Wiel. - ibid., p. 303). and from Cochin China of an epidemic among the French garrison at Fort Tongkeong in 1864 (Lange - "De la diphtherie. Relation d'une épid. de cette malad. observ. à Tong - Keon," Montp., 1869); it is stated also by Laure ("Hist méd. de la marine francaise," Paris, 1864, 15) that diphtheria was very common in the French fleet from 1859 - 62 in the China and Cochin China seas, that in one ship it was epidemic, and that the same fate overtook the crew of a United States man - of - war cruising in Chinese Waters (Gray - "Amer. Jour. Med, Sci.," Jan. 1873, 80). In the northern provinces of China, and at Pekin in particular, the malady appears to have been epidemic since 1821; there was according to Dudgeon. a terribly malignant epidemic of it in the beginning of 1866, the number of deaths in Pekin being estimated at

25,000; but its extension thereabouts is a matter of considerable uncertainty but there is no reason to doubt but that it has been common enough ever since (Morache - "Ann. d'hyg., Jan., 1870, 57; Gray - loc. cit. Lendesdorf - "Nachrichten," 1875, 9, 15; Dudgeon - "Glasg. Med. Jour.," July, 1877, 321). During this time, however, the southern ports of China seemed to have enjoyed a complete immunity from the disease. In Japan, prior to 1877 only sporadic Cases had been seen; in that year the disease became epidemic for the first time at Jokohama (Godet - "Etude sur l'hygiène au Japon Paris, 1880, 62; Scheube - "Virchow's Arch.," 1885,Bd. 99, 371), where according to Baelz (Infections. in Japan," Yokohama, 1882,5) many cases were observed in 1881and 1882. In Australia, prior to 1837, according to Dempster ("Prans. of the Calcutta Med. Soc.," 1837. 7, 357), there had been only occasional epedemics of malignant sore throat; but the disease became more or less generalised from 1858 to 1859. It appears doubtful as to the origin of this pandemic, some thinking that it had come From Tasmania ("Trans. Epid. Soc.," 1860, 1, 8; "Lancet", Nov., 1872,"Lendesdorf's Nachrichten," 1869, 1874, 8, 78; 1875, 9, 51; 1877, X1, 49), traversing the colonies of the southern littoral, others not; however occurring it is certain that the disease was productive of a very high mortality in Melbourne from 1859 to 1861, and thereafter (to 1875) in Sydney and Adelaide. The disease broke out as an epidemic in Tasmania in January 1859. (Moore - "Brit. Med. Jour.,"

Oct. 1859, 857; Hall - "Trans. of the Epidem. Soc.," 1865, 2, 78) at two places in the interior simultaneously; the epidemic seems to have lasted a considerable time, spreading to New Plymouth in New Zealand in 1861 ("Med. Times and Gaz., April, 1862). Regarded, the variety of opinion vaunted with reference to the nature of the disease, it has already been noted how Aretaeus of Cappodocia Gave an admirable picture of the malady in two Categories, viz., Angina benigna and Angina Maligna, describing also its occasional invasion of the respiratory tract and production of fatality by asphyxiation; the frequency with which it attacks children, and many points in connection with its geographical distribution. The researches of Aetius, of Armida, we have seen are remarkable chiefly for his recognition of palatal complication, and with the exception of Galen and Aurelianus he appears to have been the only one who scientifically described the disease at this time; so that our knowledge regarding it underwent no advance until the sixteenth century, when owing to its great prevalence, the malady came to be submitted to closer scrutiny. The angina was now regarded as a disease quite distinct from the ~~laryng~~ laryngeal affection, and the membrane as a scar formation. this theory, however, being upset by Home in 1765, to be replaced by the supposition of the false membrane being merely accumulated mucus. and the laryngeal affection a peculiarity of pathogenesis to

which he gave the name "Croup", but did not, however, distinguish from it "false croup" and laryngismus stridulons. From a study of the New York epidemic of 1770 Bard came to the conclusion that angina and croup were one and the same affection locally manifested, but in spite of this the older views of the separate nature of the two affections continued to be held almost every where until 1821 when Bretonneau gave to the world his celebrated monographs on diphtheria under the name of "phlegmasie diphtheretique" or "inflammation pellicu-laire." His views regarding the disease, based upon quite a monument of painstaking investigation were to the effect that croup was but an extension of the disease previously known as malignant or gangrenous angina; and that the process was not a gangrenous one, the membrane not having the nature of a scar but being made up of fibrin. Bretonneau regarded the disease as a distinct entity. - quite independant of other pseudo-membranous affections or with laryngismus stridulons,- and to it he gave the name "diphtheritis, and regarded it as contagious, and stated that he was unable to reproduce it in Animals.

The present name "Diphtheria" was given to the disease by Trousseau, who regarded it as a general constitutional affection, capable of producing death, not only by suffocation, but systemic poisoning, the membrane being not a primary lesion but a local consequent of general infection, which latter also is capable of producing the complications observed.

Virchow and others, however recognised three forms of inflamation: the calarrhal, the croupous, and the diphtheretic The croupous was considered as essentially consisting of asmall-cell formation upon the mucous membrane of the affected part; diphtheria as affecting the submucous layers, the diphtheritic exudate necrosing more and more after the manner of gangrene.

With the discovery of the diphtheria bacillus by Klebs and Löffler (1884) the true nature of the disease in all its manifestations came to be at once recognised and even more firmly established with the successful treatment of the malady by Antitoxin in 1892, so that diphtheria is now one of the diseases concerning which our knowledge is in every respect beyond the most sanguine expectations.

ETIOLOGY.

PROPAGATION.-

Diphtheria is to be encountered almost everywhere; cities are seldom or never free from it. It occurs either in the form of epidemics or sporadically, such cases being due to the ability of the bacillus to remain latent for a variable period. No matter how difficult to account for isolated cases at first, direct infection from another can nearly always be traced, for that is the only method by means of which propagation can take place; usually it is either directly from inspiration of the contagion with the air of sick-rooms, or indirectly by close contact as in kissing, proximity to a sneezing or coughing patient, and so forth. A common cause of general outbreaks seems to be from the overlooking of mild cases unattended by constitutional symptoms or chronic cases in which the lesion may be in some hidden part, the nose, for instance. Again, contact with various household objects may propagate the infection, as also by means of the hands and clothing of the medical attendant and nurses; the crowding of children in schools, infirmaries, and the like. In this connection it is interesting to note that it has been the practice of the New York Board of Health to plot upon a city map the location and date of every case of diphtheria

in which the diagnosis has been settled by bacteriologic examination. After several months of such procedure, the map comes to present a very striking appearance. Thus wherever the densely settled tenements were located, the marks were very numerous, while in the districts occupied by private houses a very few cases were indicated as having occurred. It was also apparent that the cases were far less abundant, as a rule, where the tenements were in small groups, than in the parts of the city where they covered larger areas. At the end of six months there were square miles in which nearly every block occupied by tenements contained marks indicating the occurrence of one or more cases of diphtheria, and in some blocks from fifteen to twenty had occurred. As the plotting went on, from time to time the map showed the infection of a new area of the city, and often the subsequent appearance of an epidemic. It was interesting to note two varieties of these local epidemics: in one the subsequent areas evidently were from neighbourhood infection, while in the second variety the infection was as evidently derived from schools, since a whole school district would suddenly become the seat of scattered cases. At times, in a certain area of the city from which several schools drew their scholars, all the cases of diphtheria seemed to have occurred in families whose children attended one school, the children of the other schools being for a time exempt.

MILK. -

The propagation of diphtheria has from time to

(To face p. 42).

TABLE SHOWING DIPHTHERIA EPIDEMICS DUE TO MILK CONTAMINATION.

Date.	Town.	Reported by.	Reference.	Total number of cases.	Cases among drinkers of infected milk.	Deaths.	Was the disease present among the milk handlers?	Remarks.
Nov., Dec., 1882 to Jan., 1883	Hendon	Power.	Lancet, 1883, II, i, 145.	79	55 ?	..	No.	Seven-tenths of the houses attacked had suspected milk supply. Cans were washed in sewage-polluted water
April, 1883.	London (suburb).	Mackenzie.	B. M. J., 1883, I, 874.	9 houses	9 houses	..	No.	Occurred in scattered houses.
1883	Cardiff.	Paine.	Ibid., 1883, I, 873.	....	...	..	No.	Diphtheria among consumers of a certain milk. The milk at the dairy contained an excessive amount of sewage. After closing the well there was no more diphtheria.
Dec., 1883.	Devonport.	Parsons.	Ibid., 1883, I, 878.	31	31	5	Yes.	Early in December diphtheria occurred in a house next to the dairy the privy of which was separated only by a partition from the room where the milk cans were washed.
Oct., 1886.	Yorktown and Canterbury.	Power.	Practitioner, xxxix, 85.	140	124	16	No.	Ninety-three per cent. attacked between October 8th and 18th.
June & Aug., 1886.	Melrose.	Clark.	B. M. J., 1887, cxviii 100	23	23	..	Yes.	Milk obtained from a family in which diphtheria existed.
June & Aug., 1886.	Malden.	Clark.	Ibid., 1887, cxvii, 100	27	13	..	Yes.	Source of milk same as in Melrose epidemic.
Oct. 10 to 14, 1886.	Frimley.	.....	Milch Zeit., 1886, 835.	...	70	15	...	Thirty families involved. Milk from a high-class dairy; no trouble there.
May to Aug., 1890.	.....	Jonsberg.	Jahr. d. Ges. Med., 1890, II, 208.	16	6	..	Yes.	Three cases, probably arose from visiting a girl sick with diphtheria at a milk store.
Dec., 1890. Oct. to Dec., 1892.	Surbeton.	Coleman.	B. M. J., 1891, I, 44.	27	27	3	No.	Twenty houses invaded.
Oct. to Dec., 1893.	Croydon.	Philpot	Ibid., 1894, I, 476.	97 houses	65	..	No.	2/10ths. per cent. of houses invaded, and 12% of houses supplied by contaminated milk invaded. Three cows with eruption on teats found at farm.
June to July, 1893.	Highstown	Hunt.	N. J. Bd. of H. Rep., 1893.	51	43	12	Yes.	Boy employed at dairy had diphtheria

time been traced to milk and, considering the excellence of that medium as a hatching ground for the bacillus, the fact is not surprising. Kober (Amer. Jour. Med. Sci., May, 1901), for instance, in thirteen out of thirty-six epidemics was even able to trace dairy infection, the milk in every case being handled by the diphtheria patients at the respective establishments. The following table by R.G.Freeman, of New York ("Med. Rec.," Mar. 28, 1896) is therefore of special interest in this connection:-

DOMESTIC ANIMALS. -
The disease which occurrs in cats, birds, &c., closely resembles diphtheria in man, is probably altogether of different bacteriologic origin. Much attention has, however, been given to the investigation of an infectious diphtheric affection which occurs in the oral anapharyngeal mucons membrane of hens, ducks, geese, pigeons, and other birds (Nacati - "Compt. rend.," 1876,TI, 88, No. 6; Trasbot - "Gaz. med. de Paris," 1879, p.244; Meqnin - ibid., p.253; Friedberger - "Zeet. f. Thiermedicin und Vergl. Pathol.," 1879, V,161), producing great mortality amongst them, especially of the younger birds and the finer breeds, and which is certainly propagated ~~repeatedly~~ by contagion, that is, from bird to bird. Experiments repeatedly undertaken to produce the infection by inoculation have usually failed, but Liminer ("Bayer. Med. Intellig.," 1881, No.31, p.333) and Gerhardt ("Verhand. des Ziverten Congresses f. innere Med.," Wiesbadan) claim to have been able to convey the disease to man in that way: this however has failed to obtain substantiation at the hands of others. Megnin states that he has performed autopsies upon the bodies of some three hundred fowls dead from diphtheria in his own house, bu t no case of diphtheria occurred amongst the children or other inmates, all of whom were in the habit of eating the fowls so dissected.

INSANITARY CONDITIONS. -
Great has been the controversy in the past as to the influence of insanitary conditions upon the

occurrence and epidemic diffusion of diphtheria, many holding that the disease, like other infective processes is materially influenced by such factors, if not in its origin yet in the extent and virulence of its manifestations. Some too, insist that the disease occurs chiefly and in the largest amount where organic decomposition-products offer to the bacillus a suitable soil for its development or its reproduction, or where they so affect the human organism as to predispose to the disease. The accumulation, therefore, of animal or vegetable exuviae in or upon the soil around dwellings or within them, the overcrowding of rooms along with a want of cleanliness and ventilation, or other like insanitary conditions, have all been regarded as favourable to the fruition of the germ. In support of this also is the fact that diphtheria is especially fatal to those classes of the population which are most exposed to these influences, that is, the poorer labouring classes. This matter has been carefully investigated by practitioners everywhere, and its truth emphasized by various writers, notably by Hart (loc. cit.), who states that zymotic ~~poisons~~ disease is mostly bred by poverty out of uncleanliness, and that diphtheria follows a general law of what may be termed the phytogenesis of zymotic poisons in this respect. It takes up its abode by preference in the hovels of the poor, where the stagnant and pent-up air reeks with animal effluvia - where human beings and domestic animals live like pigs together; above all - and this

is the centre towards which all sanitary precautions should ever tend - where the poisonous cess-pool and the unflushed privy taint the air with subtle effluvia, that seize their victims, as it were, by the throat, and bring death forthwith. The extreme tendency to limited action, which marks these epidemics, and which we have fully illustrated in the French Epidemics, as also in the English, may be taken as indicative of domestic predisposing causes, amongst which foremost are the nuisances referred to.

To this theory, however, there have been many objections, some holding that they have found no positive evidence in its favour. Some, moreover, contend that diphtheria assumes epidemic proportions just as often apart from the noxious influences in questions, those very localities and those classes of the people escaping its epidemic inroads in which the insanitary conditions had been most pronounced. Thorsen remarks, with reference to the Norwegian epidemic of diphtheria in 1853, that bad sanitary conditions, such as unwholesome, damp, dingy and cramped dwellings can add to the malignancy of the disease no doubt; but that it may be seen breaking out and assuming the worst type under circumstances the most favourable, while in small and poverty-stricken huts it runs sometimes a perfectly mild course. So also, during the English Epidemics from 1859-72 ("Thirty-fifth Annual Report of the Registrar General," 1875, App. XXIX) diphtheria was more fatal in the healthy districts than elsewhere. Exactly

similar was Beckler's observation ("Bayer ärztt. Intellig.,"1868, No.47, p.614) of the virulence of the disease in the farms and hamlets of the Bavarian Highlands. Referring to the incidence of the disease among the affluent and the necessitous classes respectively, Rumsey had long ago noted, concerning the epidemic of 1793 in Chesham, that there was no material difference in the number of cases among the rich and among the poor. The same fact is also emphasized by numerous observers elsewhere. Thus Capelle (loc. cit., April, 1862, p.376; Oct., 1818, p.107), writing of the Holland epidemic of 1859-61 remarks that at one place it was mostly the poor, and generally speaking those living under less favourable sanitary conditions, who were attacked by the disease; while at another place it was exclusively the well-to-do. So also, Seitz (loc. cit.) noted in Munich that the disease had existed for years among all classes of the population both rich and poor, in families belonging to the aristocracy as well as in those belonging to the working class. Geissler (loc. cit.) too, dealing with diphtheria as he observed it in the Kingdom of Saxony has aptly said that it would, indeed, be labour lost to seek for the source, or at all events the nourishing soil of diphtheria, in filth and want of cleanliness; the much abused phrase "Social misery" which comes to the front regularly whenever etiology is at its wit's end, is misapplied in the case of diphtheria; and that even our sanitary officials make express reference in their reports to

the frequent occurrence of the malady under the most favourable surroundings, therein confirming the earlier statements of many impartial practitioners in other countries. The disease, moreover, is by no means a stranger to the palaces of royalty; and frequently too, the number of sick has been considerably greater among the well-to-do classes than among the slum population; thus, according to Neucourt's account of the Epidemic at Verdun in 1850, the cases among the well-to-do section of the populace exceeded those among the poor in the ratio of 15 to 4; and during the epidemic at St. Mary Cray in 1859 Heckstall Smith observed that cases of diphtheria occurred in all ranks of life, but in a very larger proportion amongst the middle and upper ranks than amongst the poor, the exemption of the pauper class being remarkable. Odriozola, moreover, states that, regarding Lima, it was natural to expect that the disease, on making its appearance there, would find most of its victims among the poorer classes of the community, as it had done in many parts of Europe where it had raged with equal virulence: but the rrsult was just the opposite, - it was mostly those who enjoyed all the good things of life that took ill, and that preference was so marked that in the hospital for men not a single case of diphtheria occurred, and only two cases of the disease were received into the hospital for women. If further evidence in support of our contention were needed it might be remarked that, in the United States,

the negro children, who live under most insanitary and generally unfavourable conditions, have enjoyed a striking immunity from the disease. So also the JewishCommunity have remained almost exempt from diphtheria epidemics, notwithstanding the bad sanitary conditions under which the vast majority of them live. It may, therefore, be allowed that whilst certain insanitary conditions have a certain amount of predisposing influence towards the disease the latter requires, as absolutely essential to its origin, the specific bacillus.

PREVALENCE ACCORDING TO SEASON. -

Concerning the influence of season and climate upon the prevalence of diphtheria the controversy has been great. The history of the disease clearly indicates that it is prevalent under all circumstances of climate, in the highest as well as the lowest altitudes, on the coast as well as in the interior. At the same time, however, its predominence in the temperate and cold regions compared with its rarity in the equatorial and subtropical regions, is great enough to be significant, even assuming that these differences are only in part real and in part to be accounted for by the defective data from the countries of the latter class, and that a more intimate acquaintence with them than we now possess might show a not inconsiderable extension of the area of prevalence of the disease.

An approximate means of estimating the dependence

of diphtheria, as regards extent and frequency, upon the meteorological characteristics of the climate may be got from the relation of the sickness to influences of season and weather. In 126 epidemics observed the outbreaks reached their height:- 32 in Spring; 24 in Summer; 30 in Autumn; and 38 in Winter. The following table showing the percentage of all cases of diphtheria at various places (the first line - Sweeden - being all of diphtheria and the rest fatal cases only) gives a similarly result:-

TABLE OF THE PROPORTIONS OF DIPHTHERIA IN ALL SEASONS%

LOCALITY	REFERENCE	PERIOD	SEASON			
			Jan. to March.	April to June.	July to September	October to December
Sweden.	"Sveriges Sundhed. Berättelse."	1861-70	31.0	20.9	19.0	29.1
Berlin.	"Statist. Jahr. f. die Stadt Berlin."	1876-83	24.2	21.4	22.1	32.3
Saxony.	Geissler - (loc. cit.)	1873-78	28.7	17.6	17.7	36.0
Hamburg.	"Ber. d. Med. der Stadt Hamburg."	1873-82	23.9	24.2	21.7	30.2
Gottingen	Reinecke - (Loc. cit.).	1878-82	33.5	22.4	19.5	24.5
Schleswig-Holstein.	Bockendakl - "Sanit-ber. f. d. Pro. Sch. - Hol."	1872-81	29.6	20.0	22.0	28.4
St. Petersburg.	Sentz - "Pet. me. Wo.," 1883	1878-82	24.7	23.1	20.9	32.3
Frankfort-on-the-Main	"Statist. Mitth. etc., Frankfurt-a.-M."	1863-83	27.3	24.7	19.6	28.4
Vienna.	Monti - "Ueber Croup und Diphth.," Wien, 1884, 135	1863-83	31.3	23.5	15.7	29.5
Philadelphia	"Trans. Pensylvania State Med. Soc.," 1876, p.290.	1868-75	24.0	21.4	18.5	37.1

According to this table the maximum of sickness at all places occurred in the colder months, and the minimum in the warmer. It is in keeping therewith that in many epidemics an increase of the disease-area and in the number of cases has been found to take place under the influence of cold and wet weather. Thus Bonrgeois (loc. cit.) observed at St. Denis, in 1827, a striking change in the cases of diphtheria for the worst when cold and damp weather set in. According to Gibbon, during the diphtheria epidemic of 1844 at Salem, New Jersey, not infrequently the disease, after having almost subsided, would be aggravated by changes in the weather; an unusually damp atmosphere almost invariably aggravated the symptoms, while a few days of clear dry weather almost as invariably diminished their violence. So also, according to Mazier, during the epidemic of 1850-51 in the Department Orne, great changes of temperature always brought an accession of the disease.

These facts whilst of obvious value must be qualified by other considerations:-

(1) That in a very large number of cases the epidemic, once it was developed and had lasted some time, has gone on quite regardless of changes in the season and weather. Thus to particularize, it is stated by Bouillon Lagrauge(loc. cit.) with reference to the epidemic of Seine -Oise, from 1857-58, that the disease kept a uniform type under all kinds of weather; and Daviot (loc. cit.) notes the same of the epidemic of 1841-44 in the Saone-Loire and Nievre. Tueffert mentions that the malady during the epidemic of 1863 in

Etupes was just as widely spread in the hot and dry month of August as in the damp and cold months of February. According toMcKinder, the Epidemic at Gainsborough continued from 1857 to 1858 without its type being influenced in any way by the changes in the weather. Maulhardt found that the disease dur ing the epidemic of 1865-66 at Treffurt had quite the same characterein mild as in rough weather. Grau says that the epidemic in Sontra and vicinity from 1864 to 1866 underwent accessions sometimes in dry and warm weather, ~~and~~ sometimes under great cold and snow, and sometimes ~~in dry and warm weather~~ and sometimes, when the atmosphere was cool and charged with rain. According to Morelli and Nesti, the disease in Tuscany from 1862 to 1872 had been equally prevalent at all seasons, and in all kinds of weather. Jewell (Amer. Jour. of Med. Sci.," July, 1864, p.108), also remarks how, regarding the epidemic in Philadelphia in 1863, it was quite certain that neither the heat of the summer nor the cold of winter had exerted any influence in abating the virulence of the disease. Furthermore, in the epidemic of 1874 to 1878 in Persia, the disease broke out at the beginning of August, 1874, in Shiraz (29° N.,i.e., within a few degrees of the tropics); in the spring of 1876 at Ispahan, Tauris, Teheran, &c.; in the beginning of summer at Khum; in the autumn at Asterabad, Kermanshahan, &c.; and in the winter of 1877-78 in the Persian Transcaucasia.

(2) That the climax of the epidemic has very often

been reached not merely at the time of warm and dry weather, but even in the season of maximum high temperatures, or in the hot summer months; it is precisely in tropical regions where that circumstance has been particularly often noted, some writers going so far as to conclude from their experiences that a rising temperature exerts an influence favourable to the development and growth of the epidemic. Thus, in the Paris epidemic of 1841, the number of cases increased as the season advanced towards summer; and Wooster (cited by Slade, "Amer. Jour. Med. Sci.," Jan., 1861,p.305) noted with regard to the kind of weather during the prevalence of diphtheria in California in 1856, that in that climate the air in summer becomes so dry that if an ordinary soft wooden pail or bucket be half filled with water and set in the sun in the open air for six hours, and then two quarts of water be added, it will leak through the joints of the shrunken staves above the surface of the first portion of the water: this is the kind of air in which the disease has occurred with unequalled fatality. In Algiers also, diphtheria was prevalent, in 1865, from March to July, during very hot and moist weather; in Tunis, from May to August, 1882; in Gaudeloupe from August to November, 1860; in Cochin China during September and October, 1864; and in the Bermudas mostly during the hot season. At Vera Cruz, according to Heinemaun (loc. cit.) the prevalence of the disease is not associated with any one season more than another.

According to the Report of the Metropolitan Asylums Board from 1888 to 1900 the maximum diphtheria mortality occurred in January, and the minimum in April. According to Thorne, the deaths from diphtheria in England and Wales from 1870 to 1873 were;-during the first quarter - 1000; second quarter - 819; third quarter - 847; fourth quarter - 1192. In New York (old city) the observations showed a diminution for the summer months and were as follows:- first quarter - 23,738; second quarter - 23,904; third quarter - 15,322; fourth quarter - 26,671.

From these facts there are good reasons for thinking that the circumstances of the season and the unfavourable weather associated therewith, are without direct influence on the production of the malady; and that they are of consequence merely as predisposing causes in so far as they increase the susceptibility of the individual, either by exciting the particular mucous membrane which the disease is afterwards to attack, namely the mucous membrane of the throat, or, still more potently perhaps, by bringing about an outward state of the hygienic conditions amidst which the individual lives. Conversely, therefore, the diminution of epidemic prevalence reported during the summer months can be readily explained by: the comparative infrequency of catarrhal affections of the upper repirator passages; by the better airing of dwellingswith greater time

spent in the open air; and by the school holidays occurring during summer.

SOIL AND LOCATION OF RESIDENCE. -

In spite of all that has been frequently urged to the contrary the nature of the soil in a locality does not allow of etiologic interpretation; for the disease has been observed to be as common in elevated as in low-lying places, in mountainous districts as in the level, on plains as in the valleys, on dry as on wet soil, on geological formations of every kind - on porous and hard rock equally. Nowhere has the non-dependence of the disease on such conditions as these been better shown than by the comparatively quick and great diffusion which it attained in England. Thus, according toSemple Bottomley and Sanderson (cited by Hart - "On Diphtheria: its History, &c., London, 1859) if at one time a connection could be traced between the localities invaded by diphtheria and the marshy ill-drained character of the land, the next season it was found to ravage dry and elevated places with equal rage. Thus, Brighton did not escape, Scarborough suffered, the disease swept across the marshy lowlands of Essex and the moors of Yorkshire adjoining the coast, it became established in the Thames, the mountains of North Wales and the mining districts of Cornwall. The same view has been taken by other writers who contend that geological position has little, if any, connection with the disease. The idea of a damp soil being conducive to the development of diphtheria

is negatived by experience in New Jersey, and in New York, - where the disease was as prevalent in elevated and dry localities as in low and damp, - as well as by observations made in 1862 in Pennsylvania, where the malady was much less prevalent in the valleys and along the course of the Delaware than at elevated places in a dry situation. According to Van Cappelle (loc.cit., 1862, p.59), during the Holland epidemics from 1859 to 1861, just as in England, diphtheria was encountered under no special conditions of locality, it occurred equally well on sand and loam, on high ground as well as on low moors. In Malta also, according to Julia, many low damp places escaped, while elevated, dry and breezy localities were devastated. That diphtheria can penetrate even to very considerable elevations is shown by the experiences of the Himalayan slope in India and of the mountainous regions of Peru. How little the disease is associated with any one geological formation or excluded from any, will be seen by a glance at its distribution area. ~~Geissler~~ In the Kingdom of Saxony also, according to Geissler (loc. cit., p.39), that any particular character of soil has afforded protection against the spread of the malady can nowhere be made out; thus, the basalt has saved neither Stolpen nor Oberwiesenthal, nor has the porphyry given protection to the vicinity of Grimma; equally little have the gneiss and the mica-schist

conferred immunity on the Metal Mountains, or the greenstone and clay-slate on the Voigtland. It remains, furthermore, to be noted that diphtheria has broken out on innumerable occasions on board ship, and has been observed at times to have become epidemic among the crews; that is under circumstances where there could be no idea whatever of an influence exerted by the condition of the soil. Facts of that kind have already been given in giving the occurrence of the disease on board men-of-war cruising in the Indian and Chinese waters; to which may with advantage be added the occurrence, according to Lajarte "Considerations sur l'etat sanitaire de la fregatte l'Andromagne," Paris, 1866), of numerous very malignant cases of diphtheria on board a French man-of-war during a seven months' voyage from L'Orient to China; also the observation by Mackay ("Trans. Epidem. Soc.," 1860,I,63) of the disease on board an English gun-boat in the harbour of Rio de Janeiro; besides a number of slighter cases which affected officers and men there was one severe case in a midshipman on whom Mackay had to perform tracheotomy and caught the disease himself from sucking out of the tube.

The frequency of diphtheria in newly built houses has been reported by some, but cannot be interpreted etiologically being due probably to the prevalence of predisposing catarrhal conditions under these circumstances.

AGE. -

From the various notifications made in London from 1892 to 1897 it appears that slightly more than one-third of the cases of diphtheria are under the age of five years, and somewhat less than one-third between the ages of five and ten. So far as case-mortality is concerned this is highest in infants under one year, after which there appears to be a gradual fall up to the fifth year, thenceforth a more rapid one, with a marked rise after the age of forty. Before the introduction of antitoxin the influence of age upon the case-mortality was much more serious; thus, in the institutions of the Metropolitan Asylums Board the mortality of the inmates under five was 50 per cent.; from five to ten 28 per cent.; from ten to fifteen, 10 per cent.; from twenty to forty (almost) 5 per cent.; and over forty, 17 per cent.

That the occurrence of diphtheria varies greatly according to age will be seen from the following table:-

STATISTICS OF THE NEW YORK BOARD OF HEALTH.

	UNDER 1 Year.	1 YEAR.	2 YEARS.	3 YEARS.	4 Years.	TOTAL UNDER 5 YEARS.	5	10	15
Number of Deaths	1675	4263	3807	2900	1908	14,554	3012	248	75
Percentage ofdeaths at each age among 17,889	9.3	73.2	21.2	16.2	10.6	81.3	16.2	1.3	.4
Total percentage of deaths at each age among 83,635 cases reported.	1.3	5	4.5	3.4	2.2	17.3	3.4	2.9	.09

The fact shown in the above statistical summary of the scarcity of attacks under the first year of life would point to a comparatively immunity amongst nurslings. Somewhat similar is the following table of Baginsky compiled from an observation of 2711 cases of the disease.

Age of Cases.	Number of Cases.	Percentage at Each Age.
0 - 6 months.....	15	0.55
6 months to 1 year.....	69	2.5
1 - 2 years.....	227	8.30
2 - 3 ,, ...	317	11.60
3 - 4 ,, ...	354	13.05
4 - 5 ,, ...	337	12.40
5 - 6 ,, ...	264	9.70
6 - 7 ,, ...	280	10.30
7 - 8 ,, ...	209	7.70
8 - 9 ,, ...	175	6.40
9 -10 ,, ...	146	5.30
10-11 ,, ...	101	3.70
11-12 ,, ...	80	2.90
12-13 ,, ...	65	2.02
13-14 ,, ...	73	2.60

SEX. -

Although diphtheria seems to attack more females

than males, this cannot be considered of important etiologic significance, and is probably due to the duties of the feminine members of a community rendering them more often exposed to infection and to show in consequence a higher mortality. In New York City the reverse was the case, as recently 9193 deaths were recorded amongst the males and 8820 amongst the females during a particular period. The reverse again was Baginsky's observation: 1311 cases amongst males and 1400 amongst females.

RACE.-

Owing to scantiness of date it cannot be satisfactorily demonstrated that some races are specially predisposed to contract diphtheria, whilst others enjoy a pronounced immunity to it. The statement of Odriozola (loc. cit.) that the negro race in Peru is as much protected against diphtheria as it is against yellow fever, is contradicted by Tschudi who states that it is just the children of the negroes in that country who suffer most from diphtheria; and to this view of facts support is given by the experiences of others. The inference drawn from the exemption of the Chinese during the epidemic in Victoria, Australia, that the Mongolian race has immunity, is just as little warranted in fact; for the disease the writer has elsewhere shown is very widely diffused and very malignant in the northern provinces of China, and it is common enough also in Japan. Some writers have endeavoured to show a special predisposition of the Hebrew race to diphtheria, and that from the fact that a greater number of cases are reported from the wards

in New York City inhabited by the poorer Jews. This, however, is entirely due to the insanitary conditions under which the Jews live therein. The observance immunity of the coloured races have been mentioned by Walsh (New York Med. Jour., Jan., 1898), who states that in Washington, from 1895 to 1896 diphtheria occurred in 15.25 per cent. of the 10,000 whites, but only in 4.43 per cent. of the negroes.

IDIOSYNCRASY. -

Certain persons show a marked tendency to contract diphtheria and this peculiarity has been observed to run in families. On the other hand, however, many seem to enjoy a remarkable immunity. The "Scrofulous" seem in an especial way to be afflicted with enlarged cervical glands; so too, those suffering from catarrhal or other affections in or about the upper air-passages. Nurslings, it has been noted, possess a unique resistance to diphtheria, and it has been proved by experiment that their blood is even possessed of decided antitoxic properties.

EPIDEMIC RECURRENCE. -

Diphtheria nearly always occurs, like other infectious diseases, in epidemic form: isolated cases are but seldom observed, and these mostly in the neighbour hood of places where the disease is epidemic, or as forerunners of the approaching epidemic, or, still further as straggling cases after an epidemic is over. The history of the disease, as already described, clearly shows this,

and also, it is believed, a peculiar behaviour of the disease as an epidemic which no other disease shows so well - that is the cyclic character of its epidemic or pandemic recurrences. The several cycles have extended over periods of various length, many of them only a few years, and others lasting decades. Still greater variety is shown as regards intervals between the successive outbreaks of the disease: not infrequently a period of tens of years has intervened so that the malady on its reappearance has taken all and sundry unawares. There have also been great differences in the areas covered by the disease from time to time. Sometimes it has been limited to quite a small district, occasionally even to a single place and its immediate vicinity; in other cases the epidemic has extended over enormous districts, whole States, or even divisions of the globe, thereby making a true pandemic; and it is precisely under the latter circumstances that the malady has held its ground for so long a time - especially in the more populous centres - and has so come to be regarded as endemic.

In view of this the question naturally arises as to whether the disease has what may be termed indiginous foci, that is certain places where it is definitely and permanently established, and from which it issues at longer or shorter intervals to attain a more or less considerable diffusion (after the fashion of cholera and yellow fever) whose bounds it breaks through from time to time under particular circumstances, to withdraw again to its native seats

after a longer or shorter career outside them; or whether the disease each time that it appears can be regarded as being of autochthonous origin, that is the result of the development of the specific cause on which it depends. We now know the latter to be the case, so that the former theory is untenable; it is mentioned in view of the great support which it receives in times prior to the discovery of the Klebs-Löffler bacillus.

BACTERIOLOGY.

("Verhand. des Congr. f. innere Med.," 1883)

In 1883 Klebs showed a bacillus to be invariably present in the pseudo-membranes upon the fauces of diphtheria patients; and in the following year Löffler ("Mittheilungen aus dem Gesundheitsante," vol. II, 1884) isolated the bacilli in pure culture, and at the same time was able to reproduce the pseudo-membrane upon the mucous membranes of laboratory animals; and as he did not observe the latter to suffer from paralysis he remained in doubt as to the micro-organisms being the cause of the disease. It is now known by both their names, that is the Klebs-Löffler bacillus. Both the specificity of the bacillus and its production of paralysis were established beyond the shadow of a doubt by Roux. and Yersin ("Ann. de l'Inst. Pasteur," 1888-1889), to whom also belong the credit of having introduced

the method of serumtherapy. The bacillus is never absent from the lesions of true diphtheria; it can be isolated in pure culture; it reproduces the disease in others; and produces phenomenon seen in no other disorder.

MORPHOLOGY. -

The bacillus diphtheria measures 1.5 - 3.5m. by 0.4 - 1.0 m., or about the length of the ~~two~~ tubercle bacillus and twice its diameter, and like it it is somewhat curved, with clubbed or rounded ends in addition. In spite of from two to four individuals being sometimes found in close proximity, it should be noted that the bacilli ~~is~~ never form chains. A distinctive feature of the organism is its polymorphism, the bizarre organisms so often observed being merely involution forms depending on the particular culture medium.: they are especially noticeable in old cultures, wherein the typical bacilli are seldom or never to be found. The bacilli show polar granules at the ends: from the fact of their occasional branching they probably belong to a high order of bacteria. Flagella have never yet been observed upon the bacillus, so that it may be regarded as incapable of movement; it cannot exist in the absence of oxygen. In proportion to the rapidity of growth so does the involution of the bacillus occur. The best culture medium with which to demonstrate this has been found to be Löffler's serum mixture. Using this, the celerity of involution occurs with striking rapidity during which the

the polymorphic properties of the organism can be readily appreciated. On agar and glycerine, agar - agar, however, the growth of the bacillus is slow indeed, and it is now noticeable as short spindles or lanceolate forms. Wesbrook ("Trans. Assoc. Amer. Phys.," 1900, and "Trans. Amer. Pub. Health Assoc.," 1900) describes numerous morphologic types of the bacillus, and from the appearances presented draws conclusions regarding their virulence. In this he is seconded by Gorham ("Jour. of Med. Research," N.S., vol. I, p.201, 1901), but opposed by Denny (Amer. Pub. Health Assoc. (New Orleans) Meeting, 1902). Wesbrook contends that the rapidly growing bacilli with clubbed ends and polar granules are in reality virulent forms; the slowly growing, uniformly staining forms, non-virulent bacilli. Denny regards the uniformly staining bacillus, when it develops in blood serum cultures, as the pseudo-diphtheria bacillus, and, therefore, an entirely different bacterium.

STAINING PROPERTIES. -

Aqueous solutions of the aniline dyes are readily taken by the bacillus; and the beauty of appearance attained by Löffler's alkaline medium cannot be surpassed: it consists of:-

Saturated alcoholic solution of methylene - blue. 30

1 : 10,000 aqueous solution of caustic potash... 100

For this, however, an aqueous solution of dahlia may be substituted as first suggested by Roux ("Ann. de l'Inst. Pasteur," 1888, II, p.629, 1898, p.640). Another excellent method of staining is that of

Neisser, the procedure being as follows:-

Immerse the prepared cover-glass for from two to three seconds in:-

Alcohol(96 per cent.)	20 parts
Methylene-blue	1 part
Distilled Water	950 parts
Glacial Acetic Acid	50 ,,

Thereafter, for from three to five seconds in:

Bismark , br_own	1 part
Boiling distilled water	500 parts

The diphtheria bacilli will appear br_own with a dark blue polar granule at one or both ends; the pseudo-diphtheria bacilli, however, display no polar bodies. Park ("Bacteriology in Medicine and Surgery," 1900) contends that neither the Roux nor the Neisser staining solutions give any more information than the Löffler stain regarding the virulence of the bacilli. The bizarre forms of the bacillus are particularly noticeable when cover-glass preparations are stained with these solutions, and the contrast between the polar granules, which colour intensely, and the cytoplasm of the organism, which stains only very slightly, is par_ticularly striking. Correctly observed, it is quite impossible to mistake the bacilli for dipliococci. To isolate the bacilli in sections of tissue Weigert's fibrin method gives the most satisfactory results, but definition is also satisfactory attained by Grain's method likewise.

METHODS OF CULTIVATION. -

Any ordinary culture medium will suffice for the growth of the diphtheria bacillus; and plate cultures

are quite superfluous. Hence particles from the infected throat may be taken by a swab or platinum loop, and conveyed direct to tubes of Löffler's blood serum mixture. In the first tube a confluent growth of the bacillus will in due course be observed; but upon the third it is usually easy to find scattered colonies suitable for transportation. Löffler has shown that the rapidity of growth may be materially hastened by the addition of a little glucose to the culture medium; the latter bearing his name - the Löffler blood serum mixture - is made as follows:-

Blood serum .....3 parts

Ordinary bouillon+1% of glucose....1 part.

This medium is perhaps the best that can be used in the study of the disease, and is treated in the ordinary way by being run into tubes, coagulated and sterilized.

According to Michel ("Centralbl. f. Bakt. u. Parasit.," Sep.24, 1897, Bd. XXII, Nos. 10 and 11) the development of the culture can be made much more luxuriant and speedy by using the serum of the horse instead of that of the calf or ox as hitherto. The suggestion has, furthermore, the recommendation of convenience in that the horse's blood can be easily obtained by introducing a trocar into the jugular vein: the requisite amount (up to 5 litres) can be drawn without inflicting any injury or inconvenience upon the animal.

To effect a diagnosis in a case of suspected diphtheria or to obtain the bacillus in pure culture

it is merely necessary to swab some of the false membrane from the throat (a sterilised platinum loop or absorbent cotton being used), and to smear with it the surface of three, or more, of the blood-serum mixture tubes. The latter are now placed in an incubator, at a temperature of 37° C., for twelve hours; after which, if the diphtheria bacillus be present a yellowish-white layer will be found upon the first tube, the same with outlying colonies on the second tube, and large, isolated, whitish or slightly yellowish, smooth colonies upon the third. Examining these colonies the diphtheria bacilli will be detected as components, thereby confirming the diagnosis. Fresh colonies may furthermore be obtained by transplantation.[1] This method is particularly advantageous in that few, if any, other bacilli will grow so rapidly upon this medium, certainly scarcely a single found likely to be found in the throat.

To effect an earlier diagnosis, especially as a preliminary to the use of the antitoxin, than is possible with Löffler's method, Ohlmacher recommends that the still invisible growth be microscopically examined within five hours; following which a platinum loop is rubbed over the inoculated surface, the small amount of material thus secured being now mixed with distilled water, spread on a cover glass, dried, fixed, stained with methylene-blue, and examined.

Having found the diphtheria bacilli in the material taken from the fauces, one must beware of

dogmatism in asserting for an absolute fact that the person in question has diphtheria; and for the reason that the bacilli have sometimes been discovered in the throats of healthy persons who have somehow or other come in contact with the disease, and whose vital resistance is so great that the bacilli cannot injure them.

GELATIN. -

Gelatin is not a satisfactory medium as the growth of the bacilli upon it is slow and scanty; the colonies attain a small size only, and microscopically convey the impression of white spots with regular - sometimes indeed - borders and smooth contents. Examined microscopically they appear as yellowish-brown granules and with irregular borders. They do not liquefy the gelatine, and when punctures be utilized the growth of small spherical colonies will be observed along the track of the needle.

AGAR. -

The growth is less characteristic upon a 1 per cent., slightly alkaline, nutrient agar or glycerine agar than in blood serum; and bacilli direct from the throat grow but indifferently upon it. A luxuriant growth may, however, be obtained with pure cultures previously grown on some other medium: in all cases precaution should be exercised to secure the necessary alkalinity. The agar colonies are more translucent, larger, without the yellowish-white or china appearance of the blood-serum cultures, and more or

less distinctly divided into a small elevated centre anda flat surrounding zone with indented edges, or radiations. Agar cultures are chiefly used for obtaining pure cultures of the diphtheria bacillus by the plate method.

BOUILLON. -

The bacilli in bouillon develop a distinct, whitish, granular pellicle upon the surface, more especially when grown in air, or in an air current according to the suggestion of Fernbach. Great care should be taken not to disturb the flask more than absolutely necessary, as the pellicle is so brittle that it falls to pieces on the flask being moved, the minute fragments slowly precipitating about the vessel in which contained. At times the bacillus may be observed to occasion a diffuse cloudiness of the medium, but not being motile it soon sinks to the bottom in the form of a flocculent precipitate.

According to Spronck ("Ann. de l'Inst. Pasteur," Oct. 25, 1895, vol. IX, No. 10, p.758), both are characteristics of the growth of the bacillus in this medium, and the amount of toxin produced vary according to the amount of glucose in the bouillon. The cultures are therefore divided by Spronck into three types:-

Type A. - The reaction of the bouillon becomes and remains acid, the acidity increasing. The bacilli accumulate at the bottom of the clear liquid. The toxin-production is meagre.

Type B. - There is no change from alkalinity

to acidity, but the original alkalinity is very r ich, the bottom of the flask shows a ~~considerable~~ considerable sediment, the liquid is cloudy, and a delicate growth occupies the surface. The toxicity is very great.

Type C. - In a few days the reaction of the culture becomes acid, and then later on changes to alkaline. During the acid period the liquid is clear, with a white surface growth. When the alkalinity returns, the bouillon clouds and the surface growth increases in thickness. Sediment accumulates at the bottom of the flask. The toxicity of the culture is much less than in Type B.

Spronck considers that the varying reactions depend upon the fermentation of the glucose, and contends that cultures grown in bouillon without glucose are by far the more luxuriant and toxic. With a view to excluding as much as possible the glucose, he manufactures the bouillon from meat on the verge of putrefaction, and preferably beef.

By the addition of digested brain to the culture Zinno ("Centralbl. f. Bakt.," Jan. 4, 1902, XXXI, No. 2, p.42) was able to greatly facilitate the growth of the diphtheria bacillus and to increase its toxin-production.

BLOOD-SERUM. -

The growth of the bacillus upon blood serum is similar to that upon Löffler's mixture. According to Januszewska and Schabad, the bacillus grows well in ascitic fluid and produces no diffuse cloudiness, but a well marked deposit upon the bottom of the flask.

POTATO. -

The bacillus appears to grow well upon potato, but only when alkaline, and even then without characteristic growth, the appearance being that of a thin dry glaze near the point of inoculation.

MILK. -

Infection being frequently traced to this source, it follows that milk is an excellent medium for the cultivation of the diphtheria bacillus, in which it has been shown to grow well at as low a temperature as 68°F., but without changing the appearance of the medium. The statement of Gelpke that on albumen the diphtheria colonies manifest a salmon colour, - seen in connection with no other bacilli - has been disproved by Schabad and others. The growth of the bacillus is, furthermore, favoured by an alkalinity of the medium: this, however, is soon replaced by acidity, to estimate which lithmus milk should be used. With ageing of the culture the reaction becomes strongly alkaline, but the variation of alkalinity in question is not significant being entirely due to the transformation of the sugars.

Growth ~~of~~ on Antitoxin Serum. -

According to Januszewska , Frankel, Spronck, Schabad, and Gelpe, both the true and the false diphtheria bacilli grow quite well on antitoxin serum. This, however, is denied in part by Martina who insists that the former are unable to make any impression upon it.

PRODUCTION OF TOXINS. -

From researches made in 1887, Löffler (Centralbl. f. Bakt.," 1887, II, p.105) has described the poisonous metabolic products of the diphtheria ~~products~~ bacillus as being of the nature of luzymes. A year or so later, Roux and Jersin ("Ann. de l'Inst. Pasteur.," 1888-1889) were able to remove the bacteria from the culture by filtration and to demonstrate the presence of a soluble poison in the filtrate. Used by a method of injection this toxic bouillon was observed to produce serious effusions into the pleural cavities, acute inflammation of the kidneys, fatty degeneration of the liver, and oedema: in some cases paralysis of the hind quarters of the animal followed the injection, an animal slowly dying a few days or weeks afterwards. The activity of the toxin was found to be materially retarded by a temperature of 38° C., and to be destroyed by one of 100° C; and, still further, to be precipitated by absolute alcohol and mechanically carried down by calcium chloride. Brieger and Frankel ("Berl. Klin. Woch.," 1890,1-12) confirming the experiments of Roux and Jersin, came to the conclusion that the poison was a toxalbumin, and Tangl ("Centralbl. f. Bakt.," Bd. XI, p.379) was able to extract the toxin from a fragment of the false membrane after maceration in water.

According to Ehrlich ("Klimsches Jahrbuch," 1897) the diphtheria toxin is of a very complex nature, being also, as it exists in cultures, made up of both a toxin and a toxoid: the former is poisonous, the latter not fatal to animals. The

toxoids, moreover, have equal or greater affinity for combining with antitoxin than the toxin, and cause confusion in testing the unit value or strength of the antitoxin. In old or heated toxin all of the toxin molleculls become changed into toxins or toxoids and the poisonous quality is lost through the combining power remains.

There can be no doubt whatever but that the toxin is intensely poisonous: a filtered bouillon containing it may be fatal to a 300-gram guinea-pig in doses of only 0.0005 c.c. It is probably, however, not an albuminous substance, as it can be elaborated by the bacilli when grown in non-albuminous urine, or in non-albuminous solutions whose principal ingredient is asparagin. The toxicity of the cultures appears to attain its acme in the second week.

Only after the third week, according to Palmirski and Orlowski ("Centralbl. f. Bakt. u. Parasit.," March, 1895), is the bacillus capable of indol-production. The latter however has been entirely prevented by cultivating the bacillus in dextrose-free bouillon (Smith - "Jour. Exper. Med.," Sept. 1897, vol. II, No.5, p.546). The formation of lactic acid appears to be responsible for the acidity of the culture medium.

PATHOGENESIS. -

The presence of a false membrane upon the fauces, or elsewhere, due to a fibrinous inflammatory exudation, characterises the occurrence of diphtheria in man: it is commonest on the fauces, and next to

that in the nose and mouth, sometimes also being observed upon the genitals or abraded surfaces. Williams ("Amer. Jour. of Obstet. and Dis. of Women and Children," Aug., 1898) states that he has seen a case of diphtheria of the vulva; and others, the occurrence of the disease during the puerperium. The bacilli being found only in the pseudo-membrane, - and most abundantly in the older portions, - the disease has come to be regarded as a purely local infection, - due to the development of the bacilli upon the mucous membrane, - and one which is accompanied by a serious intoxication consequent upon the absorption of a poisonous metabolic product of the bacilli from the local lesions. Although the migration of the bacilli to the internals organs has been known to occur, this is proved by experience to be a very rare finding.

The duration of the disease is subject to considerable variation: what usually happens is that the patient recovers slowly, the false membrane disappearing to leave an inflamed surface of the affected mucous membrane behind it, on which the bacilli are to be found for weeks or months afterwards. During the actuala illness the microscope shows that the usual scant miscellaneous bacterial flora of the mucosa is quite suddenly replaced by a rich vegetation of the easily distinguishable diphtheria bacillus, which, moreover, may be the only bacterium discoverable in the culture tube. This vegetation sontinues for a few days, then gradually gives way to another flora of cocci and bacilli, and

finally the normal condition is re-established.

Frosch ("Zeit, f. Hygiene," 1893, XIII, Heft. 1) appears to have been the first to have discovered the diphtheria bacilli in the blood of the heart, liver, spleen, and kidneys. They had however been discovered by Kolisko and Paltauf ("Wien. Klin. Woch.," 1889) before that in the parenchyma of the spleen, and by others in various lesions of the deeper tissues; as well as in the organs, and, sometimes too, in association with streptococcus or other pyogluic bacteria, which same - in spite of the almost constant presence of the Klebs-Löffler bacillus - can be held as responsible for the production of the imflammatory sequelae of diphtheria.

The occurrence of ulcerative endocarditis in diphtheria has been noted by Howard ("Amer. Jour. Med. Sci.," Dec., 1894); while Pearce("Jour. Boston Soc. of Med. Sci.," March, 1898) has traced the bacillus in 1 cases of malignant endocarditis, 19 out of 24 cases of broncho-pneumonia, 1 case of empyema, 16 cases of otitis media, 8 cases of inflammation of the antrum of Highmore, 1 case of imflammation of the sphenoidal sinuses, 1 case of thrombosis of the lateral sinuses, 2 cases of abscesses of the cervical glands, and in oesophagitis, gastritis, vulvo-vaginitis, dermatitis, and conjunctivitis following or complicating diphtheria.

Diphtheria artificially produced in laboratory animals in no way differs from that in the human being, and consists, therefore, of a general toxaemia

with a local lesion. Rats are quite immune, but human beings, horses, rabbits, guinea-pigs, mice, kittens, and puppies are susceptible to diphtheria. On injection of half a cubic centimetre beneath the skin of a susceptible animal, the bacilli multiply at the point of inoculation producing there an oedematous fibrinous inflammation, with death of the animal about the third day. At the autopsy of an animal so destroyed the liver will usually be found to be enlarged, and under the microscope show necrotic foci in state of complete degeneration with the nuclear chromatin scattered about as fine granules. Any of the other organs may show evidence of a similar nicrosis, the presence of the same, moreover, being appreciable to the naked eye as minute whitish points, in none of which, however, are the bacilli to be found. It should likewise be noted that these lesions are in no sense characteristic of diphtheria as they are frequently to be observed in other intoxications. The lymphatic and adrenal glands are nearly always enlarged, and the latter haemorrhagic as well. The kidneys may show parenchymatious degeneration, but the fauces show no signs of inflamation. According to Roux and Yersin (loc. cit.) the introduction of the bacilli into the trachea through a tracheotomy wound, leads to the formation of a typical false membrane there followed, in due course, by the typical diphtheria paralysis.

MIXED INFECTIONS. -

Associated with the diphtheria bacillus, and most often when the fauces are severely affected, may often be found Streptococcus pyogenes and Stophytococcus pyogenes aureus and albus.

Blasi and Russo-Travali ("Ann. de l'Inst. Pasteur," 1896, p.387) state that in a series of 234 cases studied it was found that in 26 cases of pseudo-membranous angina due to streptococci, 2 patients died, the mortality being 3.84 per cent. In 102 cases of pure diphtheria, 28 died, a mortality of 27.45 per cent. Seventy-six cases showed diphtheria bacilli and stophylococcus; of these 25, or 32.89 per cent., died. Twenty cases showed the diphtheria bacilli and streptococcus pyogenes, with six deaths - 30 per cent. In 7 cases, of which 3, or 43 per cent., were fatal, the diphtheria bacillus was in combination with streptococci and pneumococci. The most dangerous forms met were 3 cases, all fatal, in which the diphtheria bacillus was found in combination with the colon bacillus.

Pearce ("Jour. Boston Soc. of Med. Sci.," March, 1898) relates how in 157 cases of diphtheria and scarlet fever observed at the Boston City Hospital, there were 94 cases of diphtheria (29 with scarlatina, 11 with measles, and 5 with measles and scarlatina), and seventeen cases of scarlatina - in three of which measles was also present. Of the 94 cases of uncomplicated diphtheria, the Klebs-Löffler bacilli

were present in the heart's blood in 4, twice alone and twice with streptococci. In nine cases the streptococcus occurred alone; in 1 case the pneumococcus occurred alone. In the liver the bacillus was found in 24 cases, alone in 12, and together with the streptococcus in 12; the streptococcus occurred in 27 cases, alone in 14, with the Klebs-Löffler bacillus in 12, and with the stophylococcus pyogenes aureus in 1. Staphylococcus pyogenes aureus occurred in 4 cases, alone in 3 and associated with the streptococcus in 1. The pneumococcus occurred alone in one case. In the spleen the Klebs-Löffler bacillus occurred 18 times, 15 times alone and 3 times associated with the streptococcus. The streptococcus occurred in 24 cases, alone in 21, associated with the Klebs-Löffler bacillus twice, and with the staphylococcus pyogenes aureus once. Staphylococcus pyogenes occurred twice, once alone and once with the streptococcus. The pneumococcus occurred twice only. In the kidney the Klebs-Löffler bacillus occurred in 23 cases, in 15 alone, in 5 associated with the streptococcus, and in 2 with the staphylococcus pyogenes aureus. The streptococcus occurred in 26 cases, in 19 of which it was the only organism present. Staphylococcus pyogenes aureus occurred in 8 cases, in 4 of which it was in pure culture. The pneumococcus occurred 4 times, 3 times in pure culture, and once with the Klebs-Löffler bacillus.

In the 46 cases of complicated diphtheria, the hearts' blood showed pure cultures of the streptococcus

9 times, and the streptococcus associated with the Klebs-Löffler bacillus once. The diphtheria bacillus occurred alone once. In the liver, in 10 cases streptococcus occurred alone, in the 7 cases associated with the Klebs-Löffler bacillus, and in 3 cases with staphylococcus pyogenes aureus. The diphtheria bacillus occured in pure culture in 5 cases. The spleen contained streptococci only 13 times and mixed with the diphtheria bacillus twice. The diphtheria bacillus was found in pure culture in 5 cases. The kidney contained pure cultures of streptococci in 10 cases, streptococci associated with diphtheria bacilli five times, and with staphylococcus pyogenes aureus three times. The diphtheria bacillus occurred alone in 7 cases; staphylococcus pyogenes aureus and the pneumococcus each alone once and both together once.

The clinical significance of this general infection with the Klebs-Löffler bacillus is not, however, apparent: it occurred generally, but not always, in the gravest cases, or those known as "septic" cases. It is probable that it may be due to a diminished resistance to the tissue cells, or of the germicidal pewer of the blood. In this series of fatal cases, moreover, the number of infections with the streptococcus and with the Klebs-Löffler bacillus was about even, though slight ly in favour of the streptococcus.

In cases of mixed infections the pathogenic effects of the associated bacteria will be added to

those of the diphtheria itself. The diphtheria bacillus probably begins the process, growing upon the mucous membrane, devitalized by its toxin, and producing coagulation necrosis. Whatever pyogenic germs happen to be present are thus afforded an opportunity to enter the tissues and add suppuration, gangrene, and remote metastatic lesions to the already existing ulceration.

It should be noted, moreover, that diphtheria inflammations of the throat are not always accompanied by the formation of the false-membrane; but that in some cases a rapid inflammatory oedema of the larynx, without a fibrinous surface coating, may cause suffocation, only a bacteriologic examination revealing the true nature of the disease.

THE KLEBS-LÖFFLER BACILLI IN HEALTHY THROATS. -

That the diphtheria bacilli can exist in the throats of persons unaffected with clinical diphtheria is a fact well known, and is not to be wondered at when the many conditions under which the organism can exist outside the human body is taken into account. They appear to be particularly common in the fauces of persons brought into close contact with diphtheria patients, as nurses and physicians, as well as in other occupants of an institution, children especially. Henbner, for instance, examined the throats of 100 children in a hospital which contained some diphtheria cases, and during the first three days of their admission found diphtheria bacilli in 24, but in none

of these did symptoms of diphtheria develop. Similar has been the finding amongst school children. Thus Fibiger mentions how, in a recurring epidemic in a public school, he found pure cultures of true diphtheria bacilli in the throats of 8 of the 1234 scholars examined. Examination of the throats of 330 healthy persons, who had never been near diphtheria patients, by Parke and Beebe ("Med. Rec.," August 18th. 1894) showed virulent bacilli in 8, and in 24 non-virulent or attenuated forms of the Klebs-Löffler bacilli. The former observer also emphasizes the persistence of the diphtheria bacilli in the throat long after the disappearance of the false-membrane, and states that in 304 of 605 consecutive cases the bacilli disappeared within three days; in 176, within one week; in 2 cases, within 9 weeks. Other writers testify to a larger persistance than this; and numerous are the records of recurrence or relapse of the malady.

SPECIFICITY. -

The following facts answer the objections hitherto urged against the specific character of the diphtheria bacillus:-

(1) When the diphtheric bacillus is found in healthy throats, investigation almost always shows that the individuals have been in contact with cases of diphtheria. The presence of the bacillus in the throat, without any lesion, does not, of course, indicate the existence of the disease.

(2) The simple anginas in which virulent diphtheria

bacilli are found are to be regarded from a sanitary standpoint in exactly the same way as the cases of true diphtheria.

(3) Cases of true diphtheria present the ordinary clinical features of diphtheria, and show the Klebs-Löffler bacilli.

(4) Cases of angina associated with the production of membrane in which no diphtheria bacilli are found might be regarded from a clinical standpoint as diphtheria, but bacteriologic examination shows that some other organisms than the Klebs-Löffler bacillus is the cause of the process.

(5) Workers in bacteriologic laboratories through careless manipulation of the false membrane sent for examination have been known to contract diphtheria therefrom, and those too, who have been known not to have been otherwise in contact with the disease.

But for the existence of the "pseudo-diphtheria bacillus," the specificity of the Klebs-Löffler organism would in all probability not be doubted. The former is most likely an attenuated or non-virulent diphtheria bacillus and, therefore, distinct from the latter. Boomstein ("Arch. Russes de Path.," Aug. 31, 1902) states that although he found it possible to modify the action of virulent bacilli, and bring back the virulence of the non-virulent bacilli, it was absolutely impossible to make the pseudo-diphtheria bacillus virulent. Denny ("Amer. Public Health Assoc.," 1902), moreover, mentions as his experience that the morphology

of the two organisms was continually different when they were grown upon the same medium for the same length of time, and that the short pseudo-diphtheria bacillus never exhibited any tendency to develop into the large clubbed forms characteristic of the true diphtheria organism; the chief points of difference, however, appearing to be that: (1) the pseudo-diphtheria bacillus, when grown upon blood-serum, is short and stains uniformly; (2) that cultures grown in bouillon develop more rapidly at a temperature of from 20° - 22° C. than those of the true bacillus; and (3) that the pseudo-bacillus is not pathogenic for animals. It should be noted likewise that these distinctions are, however, exactly what would be expected of an organism whose virulence and vegetative powers had been altered, either by persistent manipulation, or by unfavourable environment.

DIPHTHERIA TOXIN. -

Some mention has already been made with regard to the studies of Roux and Yersin(loc. cit.) as to the nature of the toxins produced by the diphtheria bacillus. For these experiments an extremely virulent culture of the Klebs-Löffler bacillus was used, and placed for one month in an incubator, when it was observed to undergo changes in reaction - first alkaline, then slightly acid, and then alkaline again. On the latter being well marked the culture was taken and allowed to pass through a Chamberland filter, when the culture-medium, now free from bacilli, on injection

into rabbits and guinea-pigs, was observed to produce the typical clinical diphtheria and occasion their destruction. The variation of toxicity was strikingly manifested in these experiments, and it was still further observed that two bacilli which will kill a guinea-pig in 24 hours will produce different amounts of toxin when placed under similar conditions of growth for a definite time. An estimate of the virulence of the toxin can be obtained by noticing the amount of same required to kill a 500-gram guinea-pig: usually this can be done with 0.1 c.c., but it should be remembered also that toxins are also produced of which 0.01 to 0.05c.c. will suffice for the same purpose. The toxins can, moreover, be preserved indefinitely if kept hermetically sealed and in a dark cool place. According to Park ("Report on Bacteriological Investigations and Diagnosis of Diphtheria, &c.," "Scientific Bulletin, No. 1," Health Department, City of New York), these toxins appear in composition of globulins. More than that, it remains for the future to disclose.

With due care the toxins can be produced artificially, the requisite conditions for which, judging by the experiences of numerous observers of the behaviour of cultures, are a temperature of from about 35° C. to 37° C.; a slight alkalinity, which should be from 6 to 10 c.c. of normal soda solution per litre above the neutral point to lithmus;

suitable peptone and meat for the preparation of the neutral bouillon, and a duration of growth of the culture of from five to eight days, according to the peculiarities of the culture employed. At too early a period toxin has not sufficiently accumulated; at too late a period it has degenerated. So far as is known, the amount of sugar in the meat is of minor importance, so long as the bouillon has been made sufficiently alkaline to overcome the acid produced by the fermentation of the sugar through the products of the bacilli. In neutral bouillon the sugar does not produce sufficient acid to interfere with the growth of the bacilli and the development of toxin. This can be prevented by the previous destruction of the sugar through the fermentation caused by the growth of the bacterium coli or other bacilli having a similar action. Besides the sugar in the meat, there are other substances, whose nature is unknown, which hinder a full growth of the bacilli or production of toxin. This is true of bouillon made direct from fresh meat, old meat, fermented meats, or meat extracts. Under the best conditions that can be devised, toxins begin to be produced by bacilli from some cultures when freshly sown in bouillon some time during the first 24 hours; from other cultures, for reasons not very well understood, not for two to four days. The greatest accumulation of toxin is on the fourth day, on the average, after the production of toxin

has commenced. After that time the number of living bacilli rapidly diminishes in the culture and the conditions for those remaining alive are not suitable for the rapid production of toxin. As the toxin is not stable, the deterioration taking place in the toxin already produced is greater than the amount of new toxin still forming.

PSEUDO-DIPHTHERIA BACILLI. -

The bacillus pseudo-diptthericus, discovered by Löffler ("Centr. f. Bakt. u. Parasit.," II, 105), occurs in the false membrane of diphtheria, the healthy mouth and throat, as well as upon the conjunctiva - especially in xerosis conjunctivae - where it is identical to the so-called bacillus xerosis conjunctivae, and is, moreover, regarded by certain ophthalmologists to be the cause of chalazion and chronic ulcerative kerutitis. When found in the nose and skin - which is by no means infrequent - it is nearly always in association with the staphylococcus aureus. In cases of impetigo, acne, and variola puslutes, it has been frequently demonstrated; so too, according to Kruse and Pasqnale ("Zeit. f. Hyg.," XVI, 1), it is a factor in the causation of Egyptian dysentery. It has also been observed in pneumonia, gangrene of the lung, and according to Howard ("Bull. Johns Hopkins Hosp.," 1893, 30), in ulcerative endocarditis independent of diphtheria. Many writers have endeavoured to differentiate between the diphtheria and the pseudo-

diphtheria bacilli by means of their growth in different media and morphological characteristics, but owing to the variations of the false bacterium rules adduced fail under test. What one has, therefore, chiefly to rely upon is the ability of the bacillus diphtheriae to produce toxin, a property which is entirely lacking in the case of the pseudo-bacillus, which latter, moreover, leads to no distinct anatomic lesion on being inoculated into animals. Park ("Scientific Bulletin, No. 1," Health Dept., New York City, 1895) maintains that all bacilli with the typical morphological peculiarities of the diphtheria bacillus, when found in the throat, are virulent/Klebs-Löffler bacilli, but that forms found in the throat closely resembling them, but more uniform in size and shape, shorter in length, and of more homogeneous staining properties with Löffler's alkaline methylene-blue solution, can with reasonable safety be regarded as pseudo-diphtheria bacilli, especially if it be found that they produce an alkaline rather than an acid reaction by their growth in bouillon. Whether the pseudo-diphtheria bacillus be the true diphtheria bacillus in an attenuated form we are as yet unable to say: every attempt hitherto made to bring back virulence to the pseudo-bacilli have failed; and it is only known as a saprophyte, except, as mentioned upon the conjunctiva, where it seems to be parasitic, under the name of bacillus xerosis conjunctivae.

P A T H O L O G Y.

THE PSEUDO-MEMBRANE.

Where Found. -

The distribution of the false membrane characterizing diphtheria is by no means restricted to the upper air passages, in support of which statement Holt's findings (loc. cit.) at the New York Infant Asylum may first be given. In a series of 109 cases its situation was as follows:-

(A) In 10 cases of infra-laryngeal diphtheria:- In the larynx only - 6 cases; in the larynx,& trachea- 1 case; in the larynx, trachea, and large bronchi - 1 case; in the larynx, trachea, large and to the smallest bronchi - 2 cases.

(B) In 63 cases of supra-laryngeal diphtheria:- Upon the tonsils only - 27 cases; upon the pharynx and tonsils - 18 cases; in the pharynx and naces,rhino-pharynx - 18 cases.

(B) In 36 cases both above and below the larynx:- Pharynx and larynx - 12 cases; pharynx, larynx, and trachea - 6 cases; pharynx, larynx, trachea, and large bronchi - 4 cases; pharynx larynx, trachea, ~~and large brenchi~~ large to smallest bronchi - 10 cases; nose, pharynx, larynx, and trachea - 1 case; nose, larynx, and trachea - 1 case, pharynx and trachea, but not larynx, - 1 case; pharynx, trachea, and bronchi, but not larynx, - 1 case.

Brown ("Med. Rec.," New York, June 25, 1887)

states that he found the false membrane to be distributed, in cases specially studied, thus:-
(A) Above the larynx (641 or 84.1 per cent.) :- Fauces (including tonsils) alone - 672 cases; nose alone - 2 cases; fauces and nose - 165 cases; mouth or lips alone 1 case, hard palate alone - 1 case.
(B) Involving the larynx (159 or 15.9 per cent.) - Larynx alone - 4 cases; larynx and fauces - 109 cases; larynx, fauces, and nose - 46 cases.

In 127 out of 220 cases examined by Councilman, Mallory and Pearce ("A Study of the Bacteriology and Pathology of 220 Fatal Cases of Diphtheria," Boston, 1901) the pseudo-membrane exhibited the utmost variation as to its location, thus:- Tonsils - 65 cases; epiglottis - 60 cases; larynx - 75 cases; trachea - 66 cases; pharynx - 51 cases; nose - 43 cases; bronchi - 42; left palate and uvula - 13; oesophagus - 12; tongue - 9; stomach - 5; duodenum - 1; vagina - 1; vulva - 1; skin of ear - 1; conjunctiva - 1; on tonsils alone - 7cases; trachea - 2; larynx - 3; pharynx - 1; left palate - 1; oesophagus - 1; epiglottis - 2; nasal mucous membrane - 1; in the remainder the false membrane involved several structures. All had during life been treated with the autotoxine so that the false membrane had in several disappeared.

Northrup reports that with regard to the extension of the false membrane in cases of laryngeal affection - before the use of the antitoxine - the findings at the New York Foundling Hospital was as

follows:- In 9 cases it extended from the tip of the nose to the smallest bronchioles; in 6, from the nose to the bifurcation of the trachea; in 17, from the pharynx to the finest bronchi; in 17, from the larynx to the finest bronchi; in 17, from the pharynx to the main bronchi; in 17, in the ~~p~~larynx and trachea; in 3, in the pharynx and larynx; and in 1, in the larynx only.

Structure. -

Microscopically examined, the false membrane of diphtheria to involve chiefly the surface mucous membrane, the superficial cells being embedded in a coagulated fibrinous exudate and in a state of hyaline degeneration. Sometimes indeed the membrane seems to consist entirely of hyaline cells; or again, the fibrinous exudation may be secondary or consequent upon the hyaline degeneration, the latter involving also any lencocytes which may have become caught in its meshes. In certain cases even the deepest layers may be involved in this degenerative process; so too, the walls of the adjacent capillary blood-vessels may become hyaline, the entire necrotic mass forming the membrane in question. The ~~particula~~ peculiar laminated appearance of this depends probably upon either variation in the necrotic processes or upon the varying depths affected at different periods. It will, moreover, be found on close examination to be connected to the subjacent tissues by a fibrinous recticulum, so that an abraded surface remains after its forcible

detachment. Wherever detached, the process of reformation is the same, namely, that of a coagulation necrosis, due probably to the local effect of the toxin leading to coagulation of the inflammatory exudate. According to Morax and Elmassian ("Ann. de l'Inst. Pasteur," 1898, p.210) typical diphtheritic inflammation can be induced upon the conjunctiva of rabbits by the application of strong diphtheria toxin every three minutes for eight or ten hours. In horses especially, and commonly during procedure of immunization for the production of antitoxin, it is by no means infrequent to find large hypodermic injections of the toxin to be followed by fluctuating necroses, which become infected from without and suppurate.

THE CEREBRO-SPINAL NERVOUS SYSTEM.

The changes produced in the nervous system are in a high degree characteristic of the disease, and are essentially due to the action of the toxin - not to the presence of therein of the bacilli themselves, and can be demonstrated by their occurrence after the inoculation of filtered cultures. In acute and rapidly fatal cases of diphtheria the nervous changes are frequently absent: some length of time is usually required for their development. Whilst most authorities are agreed as to the lesions of the peripheral nerves, those elsewhere in the nervous system appear to be subject

to considerable veriation. Thus, the fibres of the palatal nerves may be found to be in a state of degeneration. Oertel ("Die Pathogenese der Epidem. Dip. nach ihren histol Begrund," Leipzig, 1887) discribes the finding of capillary haemorrhages of the cerebro-spinal dura mater and of the sheaths of the peripheral nerves, as well as infiltrations of the nuclei and granulations of the anterior horns of the spinal cord. In other cases, besides peripheral nerve change, the cells of the anterior horns may be observed to be globular, deficient in processes, and with their nuclei and nucleoli indistinct. Not infrequently the cells appear to have been entirely destroyed. Hence, there seems no reason to doubt but that the toxin acts upon the spinal cord as well as upon the peripheral nerves. Using Marchi's method of staining in many instances there will be found a peculiar degeneration of the posterior nerve roots where they enter the gray matter of the posterior horns, and these lesions may safely be presumed to be etiologic of the ataxic symptoms of diphtheritic paralysis; which latter, carefully studied, may, for convenience of recognition, be divided into four groups: (1) Purely muscular changes without nerve involvement; (2) polyneuritis; (3) lesions of the spinal cord, which are either localizable in the gray matter, leading to atrophy of muscle, or involving the white matter of the cord, in a way similar to what is observed in cases of mulliple sclerosis or locomotor ataxy; (4) cerebral

paralysis due in the main to circulatory disturbances.

From long and painstaking experimentation Rainy ("Diphtheria Toxins and Motor Cells of the Cord," "Jour. Path. and Bact.," 1900, VI, 435) believes that the diphtheric paralysis is invariably associated with structural alterations in the spinal cord (as well as with peripheral nerve change), and these never fail to be observed at the autopsies of patients who have suffered from paralysis during life. Vascular disturbances may be observed, but the peculiarity of lesion essentially consists of a marked chromatolysis, increased staining capacity of the chromatic substance for acid stains, and vacuolation of the cell protoplasm : all of which cellular changes most likely occur before the nerve lesions, in the vast majority of instances at least. So far as the spinal grey matter is concerned two kinds of lesion may be observed in the majority of the cells in the anterial cornual group, that is, they may be either swollen or shrunken. In the former case, Nissl's bodies will be found to have undergone marked disintegration, the achromatic substance staining but faintly; the nuclei and nucleoli will be unchanged, and the nuclear membrane uncrumpled and, from disappearance of a greater part of the cell chromatm, very conspicuous.

During a series of cases (25) specially studied, Thomas ("Acute Degeneration of the Nervous System in Diphtheria," "Med. and Surg. Reports, Boston City Hospital," 1898, IX, 52) observed: (1) marked

parenchymatous degeneration of the peripheral nerves, sometimes accompanied by an interstitial process, hyperaemia, and haemorrhages; (2) acute diffuse parenchymatous degeneration of the nerve fibres of the spinal cord and brain; (3) little or no change in the nerve cells; (4) acute parenchymatous and interstititial changes in the muscles, especially the heart; (5) occasional hyperaemia or infiltration or haemorrhage in the brain or cord. Changes in the trophic centres of the nerve-cells, after 24 hours of intoxication, have been found by Woodhaven ("Post diphtherial Paralysis," "Lancet," 1900, II, 1482), which may, according to Mouravieff("Arch. de Med.," vol. IX, p.1108) be responsible for the changes in the peripheral nerves already described. Should these centres receive no stimulation, no symptoms will be observed, failing which Wallerian degeneration will develop.

One must not, however, lose sight of the fact that because lesions of the cord have been so often reported, they are inevitable. Thus, Arnheim ("Anat. Untersuch. über der Diphther." etc., "Virchow's Arch.," CXIX, 1890) found no change in either the medulla or nerve centres, only hyperaemia and capillary haemorrhages in the peripheral nerves and slight myositis.

Other writers report lesions of the cardiac plexus (parenchymatous and atrophic neuritis) in cases dying from cardiac paralysis. In such there will be found disintegration - or disappearence - of the myelin sheath, similar lesions of the axis cylinder, non-multiplication of the nucleus - all

essentially degenerative not the result of an irritant. In no case was the vagus (nerve and centre) affected, but occasionally some of the cells of the sympathetic ganglia exhibited pigmentary degeneration.

In certain cases, moreover, there may be found either a slight or a marked diffuse fatty degeneration of the nerve fibres of the central nervous system and of the peripheral nerves as well. (Thomas - loc. cit.).

HEART.

The heart is by no means always involved in diphtheria, but structural alterations have frequently been observed at autopsies, one of the first investigators in this direction being Hayem ("Etudes sur les myositis symptomatique," "Arch. de Physiol.," 1880), who reported the finding of granular and fatty degeneration of the cardiac muscle, and of acute interstitial myocarditis.

Following this Rosenbach (Virchow's Archiv, 1877, LXX) observed cellular infiltration of the interstitial tissue, in addition to granular and waxy degeneration of the muscular fibres; the latter had, however, been described by Bouchut (Gaz. des Hop., 1872) previously.

Granular and hyaline degeneration of the cardiac muscular fibres have been described by Huguenin ("Etudes anat. path. de la myocard.," Paris, 1890), as well as connective tissue hyperplasia,

multiplication of the nuclei, and capillary haemorrhages.

Romberg's researches in this connection ("Ueber die Erkr. des Herzmuskels bei Dip.," Deut. arch. f. Klin. Med., 1891, XLVIII) are both interesting and important, and show that the differences on lesions discovered vary according to the part of the cardiac muscle from which the sections are taken. Thus, by far the most common lesion found was degeneration - with occasional vacuolation - of the cardiac muscular fibre, with degenerative changes in the nuclei. In all cases examined interstitial changes were observed, which appeared to have occurred in foci, and usually beneath the pericardium, which may heal, suppurate, or lead to fibrinous myocarditis. Whilst the left ventricle is usually well contracted and the right one flabby, it is by no means unusual to find both ventricles hypertrophied and dilated. The pericardium, in Hayem's cases, showed haemorrhages occasionally, especially when sepsis had occurred; the heart muscle, granular degeneration affecting a great or small number of the fibres; the granules were fatty and albuminous, but hyaline degeneration was seldom noted. In the parts affected the transverse striations were poorly marked or absent, and nuclear changes were observed. In the right heart especially parenchymatous degeneration was noted; the base, apex, and auricles were most frequently affected: these changes were only found to any marked extent when the disease had lasted for from five to

eight days. The blood vessels were distended, - in many cases filled with lymphocytes, - swollen, thickened, and oedematous (as though boiled), but no endarteritis could be detected. In certain parts only were the round cells increased, and there enormously. An occasional capillary haemorrhage was found. Neither the nerves nor their ganglia appeared to have undergone any alteration.

In addition to degenerative changes as described in the heart muscle, Schamschin (Ziegler's Beitr., 1895, XVIII) found both the walls of the small blood vessels and their cells to have undergone degeneration. According to Papkaw (Wratsch, 1895) the fragmentation of the muscle -fibres is entirely due to the swelling and destruction of the cement substance and to the cardiac weakness seen at an early stage of the disease. On the other hand,however, Scagliosi (Virchow's Arch., 1896, CXLVI) maintains that the ordinary process is of the nature of an acute parenchymatoms myocurditis, the toxin of diphtheria first producing changes in the blood vessels, thereby gaining access to the heart-muscle itself, but seldom leading to round-cell infiltration.

Judging from the experiments of Mollard and Regnauld ("Annal. de l'Inst. Pasteur," 1887) in all primary cases the muscular fibre of the heart suffers, and sometimes, exclusively, the lesions, starting from muscle causing changes in the striations, later attacking the nuclei and cytoplasm - producing vacuolation, exudation, etc.; and eventually complete

destruction of the muscular substance. Lesions of the myocardiac blood-vessels are often seen; andit is the muscular coats of the small arteries which are particularly involved. The alterations in the smooth muscular fibres occur at the same time as those in the heart-muscle, and are, furthermore, of a similar nature. There appears, in the acute and subacute cases, to be no conspicuous hyperplasia of the connective tissue elements, beyond, perhaps, a mere leucocytosis, but the latter, if diffuse, is only an ordinary participant in the general leucocytosis which occurs in the disease. In or about the areases of muscular disintegration can interstitial nodular leucocytosis be observed: the primary lesion of the muscle induces the leucocytosis, the leucocytesis absorbing the muscular debris, particularly the sarcous exudates, so that the areas of disintegration are foci of phagocytosis.

According to thespecial investigations by Councilman, Mallory and Pearce (loc cit.), based upon an examination of the heart in 60 fatal cases of diphtheria, degeneration of the myocardium is one of the most common conditions in that disease, the simplest and commonest form being that of a fatty degeneration, seldom absent, and occurring usually in foci diffusely distributed throughout the myocardium. It is frequently observed in the form of fine granules or in large globules involving the greater part of the muscle cell; and accompanies and apparently precedes the more advanced forms of

degeneration, leading to muscle destruction. In the latter there is destruction of the sarcous elements, which are converted into hyaline masses; but in other cases large vacuoles are formed in the cell, differing in size and shape from the fat vacuoles; fragmentation and fracture of the degenerated muscle cells are often found. Simple fatty degeneration is found in the severe cases of short duration, the more extensive degenerations in the prolonged cases, all lesions being believed to be due to toxins. Acute interstitial lesions of two kinds are found. In one there are focal collections of plasma and lymphoid cells in the tissue, which may be accompanied by degeneration of the myocardium, but are not dependent upon it. In the second the interstitial change consists of a proliferation of the cells of the tissue secondary to the degeneration of the muscles, and this condition may lead to fibrinous myocarditis. Thrombosis due to the primary necrosis of the endocardium is not uncommon. Proliferation of the intima seems to be the only lesion of importance ever discoverable in the blood-vessels.

LUNGS.

It is curious in the present advanced stage of medical research that so little should have been accomplished as regards the minute changes of pulmonary lesions occurring in association with diphtheria, the energies of most observers having been almost entirely directed towards elucidation of their cause.

Broncho-pneumonia has been found at not a few autopsies. Holt (loc. cit.) indeed, maintains that some evidence, however slight, may be found of this condition in at least three-fourths of all cases examined (more especially should the lower respiratory passages have been involved during life) such frequency going far to substantiate the aspiration theory vaunted as to its etiology. Thus, Councilman, Mallory and Pearce (loc. cit.), examining 220 cases, found pneumonic lesions in 60 per cent., as follows: Of 100 cases with membrane (in epoglottis, larynx, trachea, or bronchi), broncho-pneumonia was present in 72 per cent.; in the remaining 120 cases examined, in only 48 per cent.; in 76 intubated cases, in 7 of which tracheotomy was also performed, 80 per cent.

Flexner ("Bacteriology and Pathology of Diphtheria," Amer. Jour. of Med. Sci.," 1895, CIX, 240;" The Pathology of Toxalbumin Intoxication" - Johns Hopkins Hosp. Rep.," 1897, VI) has made valuable contribution to our knowledge as to the ability of the diphtheria bacillus to produce pulmonary disease. Thus, it was found that by inoculating the trachea of rabbits with diphtheria bacilli that pneumonia

speedily followed, and it is believed to occur by durect infection as well as through the blood and lymph channels. Such experimental pneumonia, moreover, was observed to have developed from the bronchioles,- the bronchi being only moderately involved, - atria, and air-sacs, and to be of the cellular type, fibrin playing an insignificant part, and in distribution to be lobular or pseudo-lobular. In spite, however, of this experimental proof of the production of broncho-pneumonia by the diphtheria bacilli, the majority of writers maintain that having been started by the diphtheria bacilli or toxins, the further development of the pneumonic lesion in question can only be effected by other micro-organisms, such as the streptococci and pneumococci; and this for the reason that ~~in~~ the latter bacteria are alone found in many instances. This, however, cannot be accepted as proof positive of the absence of the Klebs-Löffler bacilli, the same being difficult to detect and impossible to cultivate after the pneumonia has had time to develop. Others, as Mya ("Ueber die Pattiogense der dip. Broncho-pneomonic" - Wien. med. Blatt., 1897, XX, 259, 277, 297), contend that the frequent occurrence of broncho-pneumonia in diphtheria results from the mechanical and chemical disturbance occasioned by the malady, this again, predisposing to secondary infection with other bacteria. According to Councilman, Mallory, and Pierce, the character of the anatomic lesion is little, if at all, influenced

by the particular organism concerned, for they found the pneumococci, streptococci, and diphtheria bacilli in association with serous, purulent, fibrinous and haemorrhagic exudations, necrosis, and abscess formations; but believe, nevertheless, that the pneumococcus is most often responsible for the pulmonary lesion. The diphtheria bacillus from its frequent finding is regarded by them as etiologic of the lesions in question: in 18 instances it was found alone, and under circumstances indicative of infection having occurred mainly through the bronchi, seldom by embolism, an embolic action of Klebs-Löffler bacilli being demonstrable once only. On no occasion was a true lobar pneumonia found; and even when appearances, at first sight, resembled the latter, close examination invariably revealed a confluence of broncho-pneumonia areas. The brancho-pneumonia was observed thus: In 131 cases, 27 showed involvement of only one lobe of the lung; 21 showed two or more lobes of the lung; 26 showed one or more lobes of both lungs; 57 showed involvement of all lobes of both lungs.

So far as histologic changes were concerned these authors state that the branco-pneumonia appeared to have begun as an infection of the atria, and from thence extended: it may, however, be limited to a single atrium, to lobules, or to groups of lobules. There seemed to be but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air-spaces. Acute inflammation of the larger bronchi

usually occurs, but it is not constant; whereas atalectasis and emphysema of variable extent are very commonly seen, as may also be the case with inflammatory oedema. General pulmonary oedema is, however, a rare finding. The exudation may be fibrinous, haemorrhagic, serous, or almost entirely cellular; in a few cases only is it hyaline. The cellsin the exudiation were derived in part from the proliferation of the lining epithelium, in part from leucocytes. Lymphoid and plasma cells were also found. Cellular infiltration of the interstitial tissue and productive changes in it were frequently met with in connection with the exudative lesions and apart from them. In some cases organization of the exudation and connective-tissue formation within the air-spaces was found. Proliferation of the lining epithelium or the air-spaces was frequent, and always pronounced in the vicinity of the pleura and the connective-tissue septa, which can be explained by the concentration of substances causing concentration in the lymphatics. In many cases necrosis (sometimes leading to abscesses) appears to be by no means uncommon. In the capillaries marrow-cells - frequently in a state of degeneration - were found, as were sometimes single strands of fibrin in the capillaries and interstitial tissues: never definite thrombi. The latter were, however, occasionally seen in the larger vessels. The lymphatics were commonly found to be dilated, and to contain coagulated albumin, fibrin, or cells, packed

often with lymphoid and plasma cells and large cells resembling those in the air-spaces.

SPLEEN.

The spleen is frequently found to be enlarged but not to an excessive degree. Both Bizzozero ("Beitr. zur path. Anat. der Diphtheritis" - Med. Jahrb., Wien, 1876) and Waschkewitsch ("Ueber grosszellige Heerde in den Milzfollikeln bei Dip." etc., - Virchow's Arch., 1900, CLIX, 137) have observed foci of cell infiltration in the splenic follicles, infiltration with epithetial cells, and the presence of foci of necrosis, by numerous others. In the course of an interesting and somewhat lengthy description of the splenic lesions of diphtheria, Babacci ("Neber die feineren hist. Alterationen der Milz der Lymphdrusen und der Leber. der dip. Infect." - Centralbl. f. allg. Pathol., 1896, VII, 321) states that he found the follicles more or less markedly swollen, and in most cases likewise were observed cell infiltration and cell hyperplasia, affecting the pulp about the follicle as well, in the centre of which latter were often to be seen masses of large epithelial cells, with, not infrequently, a local central or peripheral oedema. The blood vessels of the follicle usually contained little blood, seldom were distended - haemorrhages were of extreme rarity. Hyperplasia,

resulting from nuclear division of the cells and an ordinary process of Karyokinesis, was sometimes noticed: so too, necrotic areas with destruction of the cellular elements: seldom, however, was fibrin formation observed. On the other hand, it was by no means a rare thing to find hyaline degeneration of the follicular sheath, stroma, cells, and capillary walls, as well as hyaline masses in the necrotic areas, from destruction of the cells. These authors - to whom we are greatly indebted for much of our knowledge of the anatomic changes in the spleen associated with diphtheria - report that the changes found in the splenic pulp consisted in cell hyperplasia, especially about the follicles and blood vessels, and small parenchymatoms haemorrhages. True necrotic areas were not observed, and fibrin and hyaline degeneration - involving only the stroma - but rarely. In 21 out of 24 other cases of diphtheria areas of large epithelioid cells were found, but could not be as characteristic of the disease in that they were observed in 11 out of 170 spleens examined on other occasions. They are, moreover, commonly found, according to Waschkewitsch (loc. cit.) in young persons dying of ~~other~~ diseases other than diphtheria.

Councilman, Mallory, and Pearce (loc. cit.) with their usual energy and thoroughness, examined no less than 181 cases of diphtheria dying at various stages of the disease, chiefly before the tenth day, and children. In no instance were the lymph nodules

found to be of abnormal size; in two cases they were found to be markedly diminished. The most that could be regarded as abnormal was the formation of small areas of epitheliod cells, of hyaline formation, and a variable amount of nuclear detritus. The hyaline changes usually occurred in the later cases, - rarely before the fifteenth day, - and the epithelioid formation in the early ones; they were noted in 91 cases. In a few, lymphoid cells were observed between the epithelioid cells, and were probably due to proliferation of the reticular cells. The centre of the epithelioid areas were found to consist of hyaline (with remains of disintegrated nuclei) which was likewise found in the walls of the capillaries, the vessels of the foci being closed by a proliferation of their cells. In these areas there was usually a considerable amount of nuclear detritus, chiefly, however, at the periphery and within the epithelioid cells. These areas bore a marked resemblance to young miliary tubercles; in some cases the cell destruction was considerable; but there was neither caseation nor giant-cell formation. Fibrin was found in the nodules in 29 cases; and disintegrated cells in the follicle outside of the foci in question, as well as in the spleen pulp.

As regards the arteries of the lymph nodes, in 17 cases they appeared to have undergone marked degeneration, with or without the presence of foci of degeneration. These changes, however, occurring at a very early stage of the disease, were confined to the smaller

vessels of the follicles; were absent from those in the pulp; and consisted of a marked hyaline degeneration in the walls and narrowing of their lumen. The veins likewise presented alterations of the nature of lymphoid and plasma cell accumulations in the intima, leading sometimes to nodular projections into the lumen. The splenic pulp, however, in these 17 cases, showed less lesion than the follicles. More or less hyperaemia, with or without haemorrhage, was observed, in addition to increase in lymphoid cells, plasma cells, the latter being heaped in massed, and generally distributed mainly about the small veins of the pulp. This marked increase of plasma cells was only manifested in cases which had lasted for about 25 days: in a few where was observed hyperplasia of the cells lining the blood vessels, but never in the arteries and veins of the pulp. Bacteria were absent.

LYMPH NODES.

Bizzozero (loc. cit.) seems to have been the first to direct attention to the frequency occurrence of necrotic foci in the lymph nodes, and and Oertel (loc. cit,) to describe them minutely, more especially with reference to cell infiltration and haemorrhages, chiefly observable in the nodes adjoining the diphtheritic lesion. The germ centre will be found to be swollen and infiltrated with lencocytes

chiefly, however, at the preiphery, with epithelioid cells in the interior of the node, exhibiting mitosis. Certain areas may show fragmentation of nuclei, phagocytosis (the phagocytic cells being believed to be derived from the germ centres) and nuclear destruction; with areas of actual necrosis (more especially in cases showing germ centres), as well as hyperaemia, haemorrhages, oedema of the nodes, hyperplasia, lesions of the endothelium of the blood-vessels, fibrin in the glandular parenchyma, and hyaline degeneration.

Generally regarded, the lesions found in the lymph nodes and tonsils may conveniently be divided into two main groups:-

Firstly: Lesions following any kind of injury, as congestion, haemorrhage, and diffuse and concentrated necrosis. Cells extraneous to the tissue studied will be observed, and seem to be derived partly from the lymphoid cells, and partly from the proliferation of the cells of the sinuses and reticulum. The lymphoid cells will be found to be little, if at all, increased; and the swelling of the nodes chiefly results from congestive haemorrhage and dilatation of the sinuses.

Secondly: Lesions characteristicof diphtheria, but found in other infectious diseases. Here one has to deal with structural changes consisting of foci bearing a close resemblance to miliary tubercles, and formed by a process of proliferation phagocytosis, and degeneration; this large epithelioid phagocytic

cells - probably derived from the endothelium of the reticulum, and of the blood-vessels - devour the lymphoid cells and give rise to the nuclear detritus seen in the foci: the epithelioid cells subsequently undergo degeneration with the addition of their nuclei to the detritus. Caseation and giant-cell formation do not occur; and the lesion in question are not induced by the bacteria but to their toxins.

THYMUS.

According to Flexner (loc. cit.), as in lymphatic system, by experiment a process of cell degeneration may likewise be induced in the thymus gland; but it is observed to be much more widely distributed than in the case of the lymph nodes, and occurs also in foci especially noticeable about Hassall's bodies. Hyaline degeneration will be found to have attacked the blood-vessels in these cases, and the lymphaties will show dilatation.

THE SKELATAL MUSCLES.

In cases presenting fatty degenerations in the heart and nervous system, the same will be found to have occurred in the skelatal muscles.

BONE-MARROW.

Bone-marrow has, in 48 cases of diphtheria, been examined by Councilman, Mallory, and Pearce, who found it to be in a state of hyperplasia and to show changes in no way differening from those seen in connection with other infectious diseases.

PANCREAS.

In spite of the by no means infrequent observance of glycosuria in diphtheria (Hibbard and Morrisey ("Glycosuria in Diphtheria" - Jour. Exper. Med., 1899, LV, 137-147) report it in 25 per cent. of 230 patients) and the accordingly justifiable suspicion of eliotagic lesions, the observers mentioned in the preceding section, in numerous cases specially studied, failed to discover any. The same practically was the experience of Girard and Guillain ("Le pancreas dans la diphtherie" - Compt. Rendu Soc. de Biol., Paris, 1900, LII, 663-665) in 29 cases, in whom they found merely dilatation of the blood vessels together with a certain amount of endoperiarteritis and endoperiarteritis. The connective tissue showed no appreciable change beyond sometimes being slightly oedematous, very rarely indeed manifesting fatty degeneration.

STOMACH AND INTESTINES.

Diphtheritic affection of the stomach appears to be of somewhat frequent occurrence.

Five cases have been recorded by Councilman, Mallory and Pearce (loc. cit.) in which the membrane in the stomach was well developed, haemorrhagic underneath, and fibrinous in character. The peptic glands showed marked degenerative changes. This glandular lesion was observed not only in proximity to the membrane, but where the latter did not exist; thus it has been observed to extend to the duodenum. The lymphoid structures of the intestine showed the usual hyperplasia and swelling. Having succeeded in experimentally producing these lesions by injecting pure cultures of the diphtheria bacilli into dogs, Courmount, Doyon, and Pariot, conclude that the toxins of diphtheria are eliminated by the intestines. The usual believf, however, is that the slight lesions found in the intestines are the result merely of toxins circulating in the blood stream.

LIVER.

The most important research into the lesions of the liver associated with diphtheria has been made by Councilman, Mallory, and Pearce (loc. cit.) in a series of 180 cases, with the result that they describe two classes of focal necrosis:

(A) Focal necrosis (in 22 cases) about the central vein (in few or none of which extraneous cells were found) due partly to obstruction of the capillaries by pressure exerted by the secondary exudation, and partly to their occlusion by thrombi.

(B) Disseminated focal necrosis (in 7 cases) resulting from obstruction of the capillaries by fibrin, endothelial cells, and lencocytes, intermingled with which were a quantity of non-hepatic cells.

Both kinds of necrosis are believed to be due to the action of the toxin subsequent to the vascular changes. Besides these lesions there were noted both a fatty and a granular degeneration of the liver cells, slight hyaline degeneration of the capillary walls, as well as a hyperplasia consequent upon a proliferation of their endothelium and cells brought there by the blood stream. These changes, however, lose much of their particular importance when it is remembered that they do not characterize diphtheria, being sometimes observed likewise in yellow fever, amoebic dysentery, typhoid fever, malaria, and measles.

KIDNEYS.

Whilst the kidneys in all fatal cases of diphtheria show anatomic lesions, none of them can be regarded as absolutely characteristic of the disease. According to Councilman, Mallory, and Pearce (loc. cit.) they may thus be classified:-

1. Degenerative changes. - These authors observed degeneration in 112, of 171 cases examined. Fatty degeneration was, however, only slight, the degeneration of the epithelium of the convoluted tubes varying from a swelling and irregularity of the cells to complete destruction and desquamation. All cases, even the slightest, showed hyaline degeneration; and tubal casts formed by the accumulations of the granular and hyaline debris. Between the tuft and the wall of the glomerinlus a certain amount of coagulum was noticed; in some cases also swelling and hyaline degeneration of the capsules. Albumen was present in 33 cases out of 40 submitted to special investigation, and this usually was observed to correspond to the amount of degeneration found. The microscope revealed granular and hyaline casts, as well as bacteria in 61 cases, but the organisms found could not be regarded as etiologic of the degenerative changes.

2. Acute Interstitial Changes. - In 43 cases interstitial changes were found, and where most marked the kidney was appreciably enlarged. The change was most evidenced in areas towards the base of the cortex, near the pyramids, beneath the capsule, and surrounding the glomeruli. All these cases had suffered more and for a longer period than those described in the preceding section - usually for three weeks, and the most severely affected were children from 9 to 11 years of age.

In 13 cases, scarlatina complicated the illness;

in 5, measles; in 10, tuberculosis; and the urine was albuminous in 14 out of 15.

3. Glomerular Changes. - These were very noticeable in 11 cases, the initial changes being an increased cell-formation leading to projections into the lining of the capillaries, with ultimate occlusion of the latter, and the conversion of the glomeruli into a confused mass. Hyaline masses were observed in many of the lobules, with enlargement of the glomeruli; the cells of the epithelium covering them were usually enlarged, increased in number, covered the lobules like a cap, and were even seen to fill the capsular space. In two cases the latter was the seat of haemorrhage, the glomeruli being necrosed, one case being complicated by erysipelas and the other by cerebro-spinal meningitis. Cases showing these changes were older than those in the preceding classes, and the duration of the disease was usually greater. In four scarlatina was a complication; in one, measles; both diseases in another; general infection with diphtheria bacilli in two; with the streptococcus in four.

4. Haemorrhage. - This was in three cases slight: haemorrhagic nephritis was seen in one.

5. Chronic Changes. - Atrophy of the tubules and connective-tissue hyperplasia was found in four cases, apparently independent of diphtheria.

SYMPTOMATOLOGY.

Complications and Sequelae.

Classification of Symptoms.

A false membrane - characteristic of diphtheria occurring under two distinct bacteriologic conditions it becomes necessary to arrange a classification in accordance with the same at the very outset in order to allow of anything like a satisfactory description of the clinical manifestions of the disease. To one class may be assigned the phenomena occasioned by the Klebs-Löffler bacillus; to the other the membranous angina or primary inflammation of the tonsils, pharynx, etc., so frequently observed to complicate both measles and scarlatina, and due to the streptococcus pyogenes and staphylococcus - one or both. The writer, moreover, desires from the outset it to be understood that he uses the term "diphtheria" as indicative of the presence of Klebs-Löffler's bacillus, either alone or in mixed infections. The disease will furthermore be described, after Monti (Kinderheilk" - H. 10, 1900), in divisions and subdivisions, in accordance with its protean character, aš follows:-

A. According to General Characteristics:-

1. ~~Catarrhal Diphtheria (Bacteriologic Diphtheria; Diphtheril Fruste).~~

Catarrhal Diphtheria (Bacteriologic Diphtheria; Diphtheril Fruste).

2. Fibrinous or Pure Diphtheria.
3. Phlegmonous, Mixed, or Strepto-diphtheria.
4. Septic or Gangrenous Diphtheria (Septicaemia).

B. According to Localisation:-

1. Angina, Partial or Total (Angina Toxique).
2. Nasal Diphtheria.
~~4.~~ Tracheal and Bronchial Diphtheria.
~~3.~~ Laryngeal Diphtheria (Croup).
5. Bronchial Diphtheria followed by Laryngeal Infection (Ascending Diphtheria).
6. Diphtheria in Occasional Situations (Eyes, Anus, Vagina, etc.).

Incubation Period. -

As a rule the incubatory period in the case of an ordinary attack of diphtheria varies from two to seven or ten days, rarely longer. It may, however, be observed to be shorter, namely, from twelve hours to two or three days, in virulent spidemics and when the disease is produced experimentally.

Prodromata. -

The prodromal symptoms of diphtheria are far from characteristic: they may be either severe or very mild. The usual finding is that the patient complains of feeling weary and indisposed for ordinary activity, of being chilly and cold, of pain in the back, head and limbs. Young children, as in other infectious diseases, may suffer from convulsions at this period; so that the disease gives no certain

clue just now to distinguish it from many of the other children's ailmentsm, such as tonsillitis and pharyngitis. The temperature may be observed to be slightly elevated - seldom more than a degree or two. A certain degree of albuminuria may be noted; in addition to which, in simple typical cases, the child may suffer from difficulty in deglutition. The fauces may show reddening and the tonsils or palate the false membrane developing.

(A) SYMPTOMS ACCORDING TO GENERAL CHARACTERISTICS.

1. Catarrhal Diphtheria (Bacteriologic Diphtheria; Diphtheria Fruste).

In this variety of diphtheritic affection nothing beyond a mere redness and considerable swelling of the tonsils may be observed; and from it pure cultures of Löffler's bacilli may be observed. The condition will be suspected, perhaps, apart from this, by the child having been in contact with other cases either in the home or elsewhere: it may proceed to membranous formation or stop short at the slight symptoms described, the patient recovering in a few days; due no doubt to weakness of the bacillus in the present of marked vital resistance of the patient - the latter probably, as the bacilli when taken have usually been proved by experiment to be possessed of great virulence. Cases of that kind must therefore be carefully isolated as if serious, which indeed they are as regards possible dissemination of the infection. Some persons, indeed,

as doctors and nurses, may follow their respective avocations, with innumerable diphtheria bacilli in their throats, and yet, so far as symptoms are concerned, be quite unconscious of their having the disease. The fact, moreover, of not being able to discover the membrane does not prove its absence, as it may be hidden away behind the tonsil or uvula or be in some almost inaccessible situation in such as the nasal cavity.

2. FIBRINOUS OR PURE DIPHTHERIA. -

In this variety of diphtheria Klebs-Löffler's bacillus is alone concerned. The false membrane is a prominent local manifestation and there is, when generalized, the usual toxaemia from its absorption. When entirely localized, the case is benign, not so, however, should the toxins become absorbed, as it is then that dangerous complications may occur in addition to which the risk of fatality from the toxaemic condition is great.

3. PHLEGMONOUS, MIXED, OR STREPTO-DIPHTHERIA. -

There one has to deal with a mixed infection of the diphtheria bacilli and some other organism, as the streptococcus, the combined action of which and their toxins make the condition of gravity: it can,

moreover, be reproduced by experiment andits phenomena observed. Thus, if rabbits be inoculated with a virulent streptococcus from a false membrane, the animal will suffer but little inconvenience, but should Klebs-Löffler's bacillus be added death is speedy. Furthermore, such cases seem to show little or no response to antitoxin.

4. SEPTIC OR GANGRENOUS DIPHTHERIA (SEPTICAEMIA).

Cases of this class may be septic from the first; but usually, however, they are secondary to mixed infection. The symptoms of septicaemia are of the ordinary kind, and the condition is due to the combined local and general effects of the diphtheria and pyogenic organisms.

PYREXIA.

Fever in diphtheria is not a characteristic feature as in enterica for instance, but it is always advisable to submit it to careful observation in order that complications may be anticipated. The absence of fever is quite a phenomenon of fibrinous diphtheria from the lay standpoint. A carefully prepared chart will, however, show that with the commencement of the throat affection the temperature rises to attain its acme with the full development of the membrane and thereafter gradually fall, unless,

of course, the disease extends to another ~~point~~ part, in which case there will be another rise. According to the amount of toxaemia in the phlegmonous, mixed, or strepto-diphtheritic form, so will the temperature be: it is usually high and of a remittent character and continues to be so with the occurrence of complications.

CIRCULATORY DISTURBANCES.

With the invasion of the disease the pulse becomes accelerated, more especially in infants, the phenomena entirely depending upon the amount of toxins absorbed.

Abnormal slowness of the pulse, or brachycardia, is always a grave symptom in diphtheria, more especially in young children: in adults, other things being equal, it is not so serious. The correctness of this observation is confirmed by the reports of fatality by numerous authors.

Abnormal quickening of the pulse - tachycardia - is of equal prognostic importance. Thus Hibbard ("Heart Complications in Diphtheria" - Med. and Surg. Reports, Boston City Hospital, 1898) in a series of 800 cases found that less than one half with a pulse rate of 150 or more recovered, as instanced by the following tabulation:-

Pulse-Rate.	Recovered.	Died.	Percentage of Mortality.
130	436	22	4.8
130	114	22	16.2
140	85	19	18.2
150	24	16	40.0
160	18	23	56.1
170	1	7	75.6
180	1	10	90.0

Burrow's observations at the Boston City Hospital ("Clinical Study of 2093 Cases of Diphtheria" - Amer. Jour. Med. Sci., 1901, CXXI, 125-151) are equally suggestive:-

Pulse.	Mortality-rate.
110	4.8
120	6.2
130	10.1
140	20.4
150	24.7
160	29.3
170	61.1
180	72.2

According to Friedman ("Blutdruckmess bei Diphtherie," Jahr. f. Kinderh., 1893) a fatal termination may be anticipated should a marked reduction in blood pressure occur, as it indicates absorption of toxins. Intermittency of pulse is likewise unfavourable: it preceded death in 9 of the 19 cases reported by Hibbard (loc. cit.)

B. SYMPTOMS ACCORDING TO LOCALISATION. -

1.

1. Angina, Partial, or Total (Angina Toxique).

a

(a) Partial Angina. -

In this benign variety of diphtheria - the most common - the fauces and pharynx will at first be found in a state of hyperaemia and redness, more pronounced, however, at the seat of the future false membrane and wherever the mucous membrane of the part be either thickened or abraded. The tonsils are most apt to be involved in the lesion at this stage, and will present on their inner surface, and about the centre of same, a yellowish-white exudate, which increases in volume with the progress of the disease and can be readily detached without injuring the subjacent parts, following which its reformation is both speedy and more luxuriant. The membrane is by no means always located towards the centre of the tonsil, as it has been observed in various situations. It sometimes, owing to the surrounding swelling, appears as if it had actually eaten into the tonsil. According to Sevestre and Martin ("Traité des Malad. de l'Enfance," Paris, 1897) one peculiarity by no means of which the membrane can always be recognised as that of diphtheria is a thin web-like reticulum at its edges. It is very frequently mistaken for follicular tonsillitis - in the absence, of course, of bacteriologic investigation - when, instead of having a focal origin it commences at several points simultaneously, and over the site of the

tonsillar crypts. When found in connection with several crypts the membrane will appear as white points, constituting what is sometimes termed "Acute lunar diphtheria of the tonsils." This may spread over adjacent parts and develop into a severe general diphtheria. It is by no means unusual to find the primary lesion to be of an herpetic character, and to be accompanied, moreover, by a similar eruption upon the lips. Only by a bacteriologic examination - suggested, perhaps, by the subsequent paralysis - can the diphtheritic nature of the lesion be determined. Affection of the other tonsil, by direct contagion, is of somewhat later occurrence, and the false membrane, now that it is fully formed, will be seen to resemble wash-leather in appearance, tenacious and tearing with difficulty. As the disease abates, or under treatment, it, however, becomes more friable and gradually disappears, leaving a reddened, hyperaemic mucous surface.

When attacking the fauces - usually the posterior, seldom the anterior - the primary lesion can be recognised with much greater facility than upon the tonsils. Sevestre and Martin (loc. cit.), indeed, consider its appearance as pathognomonic. It is usually of a greenish-white colour, closely adherent to the underlying tissue, as well as more moist-looking, and softer than the tonsillar membrane. When located upon the back part of the pharynx, the membrane is usually found in separate patches which may never coalesce. Affection of the

uvula is always secondary to that of the tonsil, on one side only, and producing marked deviation if not surrounding. When observed upon the back of the uvula the membrane most likely is a result of infection from the nares. The cervical lymphatic glands will be found during this time to be swollen and tender on pressure.

Towards the beginning of the disease especially, constitutional symptoms may be entirely wanting, but usually the patient complains in a husky voice, of some degree of inconvenience or pain on swallowing, and, with the exception, perhaps, of some slight disturbance of pulse and temperature, together with lessened appetite and slight depression, the general health appears to be unaffected. A slight degree of albuminuria may be found, and, in rare cases, paralysis as a sequela. The adenitis is apt to persist after the membrane has become detached, and the parts returned to normal. The latter, though usual, does not, however, always occur forthwith, for the membrane may repeat itself many times, especially if irritated in any way. Sometimes, suddenly, but more often by a gradual or rapid extension of the membrane from the back of the pharynx, the larynx may become infected.

(b). GENERAL, OR TOXIC, ANGINA. -

This form is much more serious than the mild

variety just described, to which, again, but rarely, it may be secondary. The false membrane may be in colour anything from a gray to a black, and is usually both thicker and more extensive, covering the tonsils, fauces, pharynx, and uvula, the latter being often oedematous, covered with membrane, free, or bound to a faucial pillar. The tonsils, whilst invariably swollen,, may, especially in cases of mixed infection, be so much enlarged as to make nasal breathing the sole resort. The disease is accompanied by severe symptoms from the very outset, of a toxaemic character, and death, in the "typhoid" state, is by no means infrequent. The disease is at its height in from 24 to 48 hours; when the patient will be observed to be listless and apathetic, or excited and delirious. Vomiting may or may not be a feature of the illness, and tenderness, with swelling, of the cervical glands is constant. Owing to the accumulation of mucus in the naso-pharynx and general swelling of the parts, swallowing becomes extremely difficult. Albuminuria commonly occurs and to a great degree. Should the larynx and the bronchi become invaded the risk of fatality is great (independent of that, the patient may die from degenerative changes); this, however, is not so common as in the benign form as the malady usually carries off the patient before the lesion has had time to invade the larynx. The duration of the disease is a variable quantity. In simple cases, or those properly treated, equilibrium of parts may be

restored, and usually is, in from three to six days; otherwise, the disease may be protracted for six weeks.

Two other forms of angina remain to be described as of a general or toxic character, namely, the phlegmous and the septic, the latter being a proceed of the former.

(b. 1.) PHLEGMONOUS OR STREPTO-DIPHTHERITIC ANGINA. -

From the very outset of the disease the whole throat participates in the diphtherial process. It is only very rarely that the lesion commences in the tonsil and even then it is diffused with striking rapidity. In cases of this kind the severity of the affection is apparent. From the very beginning the uvula is oedematous, the cervical glands enlarged and painful, and the mucous membrane about the throat swollen and dusky-red, following which, in quick time, appears a thick, hard, discoloured, or blackish, false membrane. Its celerity of formation and marked tendency to extend distinguish this form from ~~the~~ fibrinous, or pure, diphtheria; as an additional aid to which may be noted the yellowish-red, haemorrhagic condition of the subjacent mucous membrane remaining for a time after its forcible detachment. It soon developes again, and is even more tenacious than before. The constitutional disturbance in this form of the disease is very marked. The more extensive the infection the greater will be the pyrexia. Toxic symptoms are usually very early observed. The patient appears listless, apathetic and greatly prostrated; the respirations are rapid,

and vomiting is often a troublesome complication. Early albuminuria is a constant finding: it has been observed as early as the second day. Both heart and kidneys are apt to suffer; and paralysis may occur in the lower extremities, pharynx, etc., and ocular muscles. Death may occur in various ways, e.g.: by cardiac paralysis, general infection, nephritis, invasion of the larynx and bronchi, paralysis of respiration, broncho-pneumonia, or endocarditis. The disease is, however, often recovered from in less than a week (5-6 days) when properly treated with antitoxin.

(b. 2.) SEPTIC ANGINA. -

This form of angina is an advancement upon the foregoing; is septic from the onset; seems to be a peculiarity of certain epidemics; and is of an extremely malignant character. Sudden death by collapse is common, and vomiting is of an alarming intensity and frequency. The patient may become moribund in the course of a single day. The respirations are markedly increased. High fever occurs with great suddenness and the pulse is correspondingly accelerated and weakened. The tonsils present a gangrenous appearance, the breath has an offensive odour, and the cervical glands are swollen to an enormous degree. The general symptoms are clearly indicative of septicaemia from which the

patient usually dies in the "typhoid state" on the second, third, or fourth day. This malignant form of diphtheria is sometimes, however, recovered from, but nearly always serious sequela - nervous or renal- remain. Should the parts slough off - which may happen if the streptococci be very virulent - cicatrices form. Extension of the lesion to other parts is common, and, if untreated, recovery cannot be expected.

NASAL DIPHTHERIA.

Diphtheria of the nose occurs in three forms

1. Fibrinous, or Pure, Diphtheria; Fibrinous Rhinitis.
2. Phlegmonous, Mixed, or Strepto-Diphtheria.
3. Septic or Gangrenous Diphtheria.

Each of these will require separate description:-

1. Fibrinous, or Pure, Nasal Diphtheria; Fibrinous RHINITIS. -

In infants especially, this form of nasal diphtheria may be primary: in others it is usually an extension from the pharynx.

(a) Nasal Diphtheria in Infants. -

The temperature will be found to have risen a degree or so; the infant will seem more tired and apathetic than usual, with a disinclination for nourishment and a marked tendency to sleep. The nostrils usually discharge freely - excoriating both

the ali nasae and upper lip, - and rhinoscopic examination will show the nasal mucous membrane to be swollen and reddened. The sufferer breathes almost entirely through the mouth in consequence of this; the phenomenon of "snuffling" is very noticeable; and feeding occasions difficulty and inconvenience. In a few days - should the disease persist - both breast and bottle will be refused altogether and the infant lapses into a very weak condition. Attempts at feeding, when made, may be attended with symptoms of impending suffocation; apart from that interference with respiration may be manifested in more or less continual cyanosis, especially in crying. The disease having advanced so far, if the nasal mucous membrane be examined, it will be found to be of a brilliant red colour, and to have fibrinous exudations, so great, sometimes, as to give a cast of the choanae on forcible removal - a procedure giving prompt relief to the respiratory difficulty, and allowing the infant to partake of nourishment in comparative comfort: sometimes, however, only for a time, as the membrane, and consequent disturbances, may return. Should the lesion extend to the pharynx angina - like symptoms as already described will be observed in addition to those just mentioned. The distress attending attempts at feeding and the risk of suffocation are very great; in addition to which equally serious conditions are the starvation induced, laryngeal

involvement, impediment of respiration, toxaemia and systemic depression. The mortality in these cases is very great, and the fatality is commonest about the end of the first week.

(b) Nasal Diphtheria in Older Children. -

In the nasal diphtheria of older children the symptoms are after the style of those just described, but of much less severity. Pharyngeal extension is very frequently observed. Should the choanae be almost occluded, the temperature will be elevated, snoring heard, and respiration troublesome; so that, when seen asleep the child gives one the impression of suffering from laryngitis. Nasal discharge and excoriation are, in this form, as in the foregoing one, noticeable, as also may be epistaxis and enlargement and tenderness of the cervical glands. The false membrane inside the nose is often well developed, or the nasal mucous membrane markedly swollen and red. In children the disease is usually acute - chronic in the scrofulous so that the mucous membrane recovers its equilibrum in a week or so. Should, however, the nasal lesion become so general and severe as to occlude the passage, death from toxaemia or suffocation may occur; or, again, laryngeal extension may be productive of a fatal result.

2. Phlegmonous, Mixed, or Strepto-diphtheria of the Nose. -

This form of diphtheria usually commences suddenly about the choanae, and is accompanied by much snoring and enlargement of the sub-mandibular and cervical glands. The inflammation of the nasal mucous membrane is intense; the secretion - which excoriates the nose and upper lip - profuse, the general swelling of the affected part great, and streptococci and diphtheria bacilli abundant. Should the membrane become detached, the surface will be found to be reddened: the membrane itself is thick and dark. According to the degree of lesion so will the temperature vary, accompanying which will be prostration, vomiting, apathy and other signs of toxaemia, as well as epistaxis. Cardiac and renal complications are frequently observed in a few days. The lesion may spread to the pharynx, as commonly happens. Older children are chiefly attacked by this form of the disease; and the younger the child the worse the prognosis, death being common about the fourth day, unless, of course, antitoxin be used when the disease will usually very rapidly subside.

3. Septic Nasal Diphtheria. -

Either form of nasal diphtheria may become septic in which case, owing to the abundance of lymphatic supply the chance of the patient's recovery is but small.

LARYNGEAL DIPHTHERIA, OR CROUP.

In this form of the disease the false membrane may occur first on the mucous membrane of the larynx,

and in these cases the mucous membrane of the nose and pharynx may be free from false membrane. A close inspection of the back of the palate and tonsils, may, however, reveal a slight primary membranous formation in these situations. So far as symptoms are concerned it will be found convenient to describe them in three stages:-

1. Stage of Invasion. - If a laryngoscope examination be made the mucous membrane of the part will be found to be red and swollen and from it pure cultures of Klebs-Löffler's bacilli can be obtained. The usual signs of laryngeal irritation - hoarseness and cough - will be in evidence, and, usually, for one or two days, by which time the membrane will be commencing to develop and the second stage entered upon.

2. State of Spasm. - In this stage the false membrane - from the commencement of which it dates - forms rapidly so that the larynx may show stenosis as early as the end of the first 24 hours: such rapidity, however, is uncommon. The voice will be observed to be even more hoarse than in the preceding stage, and the characteristic spasmodic cough developed. The latter is dry, short, and hoarse in character, its paroxyms lasting for several minutes and producible by trivial causes, as the patient's movements, swallowing, or laryngoscopic procedure. The spasmodic symptoms are very distressing to witness and consist of cyanosis of the face, redness and bulging of the eyes, swelling of the veins of the head and neck and perspiration. Such violent coughing, however, fails to dislodge anything

more than a little mucus - sometimes not even that. With the further development of the disease the voice almost entirely disappears, the respiratory movements become noisy, and the symptoms of stenosis more promounced, so that the breathing is of a whistling character with an interval between the laborious inspiratory effort and the harsh expiratory. The accessory muscles of respiration are now seen to be in vigorous action; and there will be seen depressions over the clavicles, at the epigastrium and about the neck. The stethescope demonstrates the prolonged character of the respirations, which, however, in contrast to other dyspnoeic conditions are only slightly increased in frequency. Attacks of asphyxia may come on very suddenly, so that the child starts up quickly and begins to cough violently. The face is observed to be livid and anxious, and to allow of breathing the child sits up with head thrown back and the body inclined forwards. On the subsidence of the spasm in from two to ten minutes the patient sinks back into bed and is found to be covered with perspiration. In these extreme cases unless relief is soon gained the child dies of suffocatiin. In many instances a slower form of suffocation may result from extension of the membrane downwards to the bronchi. Laryngoscopic examination is usually out of the question at this stage, but if it can be effected the larynx will be observed to be red and swollen, the false membrane located upon the epiglottis, in the sinus of Morgani, the trachea (rarely), and upon the vocal cords. The

latter will be observed to have merely a small opening - unchanging during inspiration and expiration - between them; and the interior of the larynx may be, as it were, plastered over with the fibrinous exudate. When coughed up - which occasionally happens - the false membrane will quickly reform, relief being obtained in the meantime: a cast of the interior of the larynx may sometimes be obtained in this way, but usually only small pieces of membrane are coughed up at a time. This stage may subside in twelve hours or be prolonged for a week.

3. Stage of Asphyxia. - This is the stage in which death by suffocation is commonest. The local symptoms and now very alarming as they are the outcome of laryngeal obstruction as evidenced by the urgent dyspnoea with a rising and a falling of the larynx retraction of the intercostal and supra-clavicular spaces the epigastrium and lower chest. But for the vigorous action of the accessory muscles the child would cease to exist. The respiration gradually becomes slower and very noisy and somewhat asthmatic. The distress of the patient is distressing to see, and appeals for help piteous. Death usually takes place during a convulsive attack and in a state of cyanosis. There are, however, cases less severe than these with intervals of comparative comfort, only of a short duration. Cyanosis may increase with each spasmodic seizure and the usual symptoms of carbonic acid poisoning be observed. During the intervals of relief the evil effect of the condition is manifested by the apathetic prostrated listless

condition of the patient, which may sooner or later develop into stupor and coma in which the patient dies. If not treated a mortality of from 95 to 98 per cent. may be expected, to which oedema of the lungs or glottis, emphysema, bronchitis, bronchial extension, broncho-pneumonia, or other complications, greatly contribute. Death in the second stage usually occurs from asphyxia. Tracheotomy, ~~and~~ intubation, and anti-toxin, have fortunately robbed the condition of many of its terrors and vastly lowered the death-rate.

Phlegmonous, or Mixed, Laryngeal Diphtheria. -

The symptoms and course of this form of the disease (secondary to nasal or pharyngeal diphtheria, alone or combined) vary with the relative virulence of the streptococcus and diphtheria bacilli. Should the latter be stronger the phenonena will resemble those of ordinary fibrous diphtheria, but, of the former, there will be destruction of the epithelium and involvement of the whole depth of the mucous membrane by the exudative process. Even before the formation of the membrane, from swelling and oedema of the parts, marked symptoms of stenosis may be observed, the same often as early as the first day. Even when the diphtheria bacilli prevail the stenotic symptoms are of slow development, so that it is a rare thing to find asphyxial attacks early in the disease. If the larynx be examined it will be found to be reddened and swollen. The epiglottis is markedly thickened, and the vocal cords, and neighbouring parts,

swollen and covered with a thick tenacious ~~false~~ false membrane; in addition to which the glottis is narrowed and tracheal exudate lies between the cords. In two or three days the condition subsides. In the second form of phlegmonous diphtheria, however, there may be no signs of laryngeal involvement, and but little cough or hoarseness; the epiglottis, whilst swollen and reddened, is free from membrane, which latter, moreover, is seldom observed except on the false cords, the true being only swollen and red. The laryngeal symptoms last longer than in the form just described, the condition being, moreover, marked by the symptoms due to the involvement of the nose and throat and resulting toxaemia. Sometimes suddenly and unexpectedly suffocation may occur, or, again, the stenosis may become worse and the patient be asphyxiated. As a rule, however, in the phlegmonous form of the disease, asphyxia occurs very often in the absence of severe stenosis. Cyanosis will be evidenced in lividity and cadaveric hue of the skin, The symptoms of mechanical obstruction may be marked by prostration, coldness, anaesthesia and pulselessness. Symptoms of carbonic acid poisoning are, however, easily recognised. Numerous are the complications met with; and quite commonly one has to deal with paralysis of the vocal cords and pharyngeal muscles, as well as degenerative lesions. Mortality is high.

Septic Laryngeal Diphtheria. -

This condition is an outcome of septic diphtheria

of the nose, throat, or both; and begins with apathy, prostration, and high fever, quickly developed, and sometimes accompanied by erythema upon the limbs or about the neck. The nose and throat present appearances resembling those described under septic angina; the cervical glands are markedly enlarged and the skin over them inflamed; and the laryngeal mucous membrane is swollen, red, and covered with a grayish-yellow exudate. The tongue is very much coated and salivation, muco-purulent offensive nasal discharge, epistaxis, labial excoriation and vomiting are frequently observed. Delirium anuria, weakness and acceleration of the pulse may develop; and the child dies in a state of septicaemic collapse. The latter is, however, usually preceded by diarrhoea and vomiting, extreme swelling of the cervical glands with surrounding inflammation, falling temperature, and rapid weakening of the pulse. In rare cases the patient recovers after a slow development of symptoms; but even then, debility, severe anaemia, renal and cardiac affections, may eventually prove fatal.

The Etiology of Diphtherial Asphyxia. -

So far as the dyspnoea in any type of uncomplicated laryngeal diphtheria is concerned four theories - the third and fourth receiving little support - have been advanced: (1) Spasm of the glottis; (2) mechanical obstruction from false membrane; (3) paralysis of the dilators of the glottis; (4) excitation of the respiratory

centres by carbonic acid poisoning with reflex action of the vagus nerve. With reference to the second theory, it cannot be said to cover all cases as the false membrane is frequently absent from the larynx, the latter being swollen and congested, and the symptoms, in these cases, indicative of stenosis by contraction of the hypersensitive larymgeal muscles. The theory of spasmodic origin of the dyspnoea is probably the correct one, as (1) the muscles of the glottis, with one exception, are constrictors; (2) sedatives relieve the symptoms; and (3) the presence of spasm is demonstrated sometimes by the "grip" of the larynx upon the tube when such be utilized as a remedial measure. To the effects of the spasm must, however, be added those of the swelling and of the false membrane upon the mucous membrane, especially at a late stage of the disease, when the coughing up of the exudate occasions marked relief.

at The "asphyxie blanche," or "pale asphyxia," seen at a late stage of the disease can be accounted for upon the following grounds:- In health the contraction of the diaphragm is coincident with the dilatation of the glottis; but in laryngeal diphtheria the latter is closed while the diaphragm contracts: the air cannot enter the lungs in sufficient quantities to inflate them, hence a vacuum is produced and the previously noted phenomena of depression in the epigastrium and suprs-clavicular regions, etc. ("tirage") appear. In addition to this, it may be noted that the vacuum causes the blood to enter the vessels within the

thorax; the peripheral vessels being thus depleted, the characteristic pallor is produced, and is always a grave symptom, and one demanding immediate treatment. The so-called pulsus paradoxicus, which occurs in modified form during attacks of stenosis, is due to the same physical condition as that just described; that is, on account of the partial vacuum existing in the thorax, the blood is drawn into it from the peripheral vessels, so that with each inspiration there is complete, or more often partial, obliteration of the radial pulse.

TRACHEAL AND BRONCHIAL DIPHTHERIA. -

This may or may not be secondary to laryngeal diphtheria; and is either fibrinous or phlegmonous. It is frequently located to the trachea, but has been known to extend downwards into the finest bronchi. In diphtheria following measles especially, one meets with the condition known as "ascending croup" : here the disease commences in bronchi and trachea, involving the larynx secondarily. The only certain sign of bronchial diphtheria is to find a membranous cast coughed up, but the condition may often be suspected if certain symptoms and signs be present. Thus, the patient usually suffers from a certain amount of continuous - not exacerbated - dyspnoea, and increase of respirations: retraction of the epigastrium, etc., is not marked, neither is prostration. Pallor of the face

and blueness of the extremities are usually in evidence. The stethescope reveals but little: perhaps a few unimportant bruits and râles. Some writers, however, attach great importance - in the absence of other conditions - to the diminution of breathing over a certain area of the chest, for it clearly indicates total or partial occlusion of the bronchus and branches corresponding to the area in question, more especially should the phenomenon be observed after removal of the laryngeal obstruction, e.g., by intubation. Bronchial diphtheria is manifestly a very serious disease, but the results obtained from antitoxin, etc., are encouraging. In cases of mixed infection the outlook is almost hopeless, the patient, in spite of treatment, usually dying from toxaemia in less than three days.

DIPHTHERIA IN OCCASIONAL SITUATIONS.

CONJUNCTIVAL DIPHTHERIA.

Whilst usually secondary to diphtheria of the nose or elsewhere, this form of the disease has been observed as a primary condition. Cases can be arranged in three classes, namely: (1) interstitial; (2) croupous or superficial; and (3) catarrhal.

(1) Interstitial Conjunctival Diphtheria. - In this form the eyelids cannot be retracted owing to the great swelling and infiltration present. The conjunctiva will be observed to be covered with a

grayish undetachable exudate, and ecchymotic. About the sixth day the false membrane begins to disintegrate, a profuse purulent discharge remaining owing to the frequency of ocular ~~discharge~~ complications blindness often ~~follows~~ occurs, but less so since the introduction of antitoxin.

(2) Croupous, or Superficial Conjunctival Diphtheria. - The symptoms and signs of this variety bear a marked resemblance to those of acute catarrhal conjunctivities. There is, however, no infiltration or stiffening of the eyelids as in the first form. The false membrane is whitish, covers only the inner surface of the lids, can be easily detached, leaving a red, bleeding and infiltrated surface. It is, moreover, seldom followed by blindness or corneal lesions.

(3) Catarrhal Conjunctival Diphtheria. - This form of the disease is even milder than the former; and membrane is absent. The secretion, instead of being of the muco-purulent character of ordinary catarrhal conjunctivitis, is scanty, glairy, and thready; the swelling is more marked; the conjunctiva less injected; the epithelium instead of being dull and desquamated, is swollen and vitreous, and this condition may be regarded as an aborted form of the second.

In all three forms of the disease virulent diphtheria bacilli are present, either in pure culture or in mixed infection with pyogenic organisms and gonococci. The first form is most apt to have

the streptococcus associated with it; the second and third, the staphylococcus.

AURAL DIPHTHERIA.

(A.) The External Ear. - Diphtheria of the external ear occurs as a secondary infection, as from scratching with the nails, or by being engrafted upon eczema or other dermal lesions. The false membrane may grow so luxuriently as to entirely occlude the external meatus, from which too, a serous or sero-purulent discharge exudes. The disease usually resolves in ten days or so; but it is by no means rare to observe an extension to the middle ear.

(B). The Middle Ear. - Diphtheria of the middle ear seems to be far more common than is usually supposed. Thus, Lommel ("Pathologic Conditions in the Middle Ear and Sphenoidal Sinuses in Diphtheria" - Arch. Otol., New York, 1897, XXVI, 150) observed it in 24 of the 25 cases specially investigated. In many instances mixed infection is present, and by extension from the pharynx via the Eustachian tube. Councilman, Mallory, and Pearce (loc. cit.) at the autopsies of 144 fatal cases of diphtheria found otitis media in 86; the mastoid cells being also involved in 13. They were seldom able to obtain the diphtheria bacillus in pure culture, from which it was concluded that the presence of these organisms was purely accidental, not etiologic of the middle ear affection; the latter being recognised during

life in only 23 cases, 6 of which developed before the fifth day, 8 between the fifth and eleventh day, the remainder after the fourteenth day, with the exception of two on the thirty-fourth day. Nasal diphtheria was present in 12 cases; and all the patients , except 3, were under 3 years of age.

The disease will be first suspected in infants, from pain followed from discharge from the ear, the latter relieving the former, and continuing as a sero-purulent foetid, or sanguineous, otorrhoea. In a few days the false membrane becomes detached from its location deep in the canal, but the otorrhoea is apt to be chronic. The usual complications of the condition may be observed.

Buccal Diphtheria.

Diphtheritic affection of the mouth is rarely encountered except in malignant cases and those of a phlegmonous character. The cheeks will be found to be covered inside with patches of thick tenacious false membrane - overlying a red bleeding surface - especially luxuriant upon the fraenum linguae, tongue, and interdental mucous membrane. The tongue is swollen and painful; salivation is frequent, and the submandibular glands are enlarged.

The disease is, however, more often seen complicating one of the acute exanthemata, especially measles, and may be observed as a primary infection, although frequently in association with the staphylococcus. The appearances present a close

resemblance to aphthous stomatitis, and the disease seldom spreads.

Diphtheria of the Genitals and Anus.

This condition is nearly always a mixed infection; secondary to diphtheria elsewhere; and occurs chiefly in young children. The vulva is most often attacked - rarely the vagina - by the lesion, which is at first patchy, soon forming a complete membrane, and spreads from the labia majora - where it usually commences - to the labia minora and vagina: extension to the uterus, anus and rectum, however, seldom occurs. The membrane if detached may return. The condition is a very painful one; there is much swelling; and the inguinal glands are markedly enlarged. The affected parts have been known to ulcerate, and even to become gangrenous. In male children the disease is somewhat less common, and attacks the glands and prepuce: rarely has urethral extension been observed. The parts usually heal quite well, though sometimes very slowly.

DIPHTHERIA IN ASSOCIATION WITH OTHER INFECTIOUS DISEASES.

1. Measles. - Measles frequebtly precedes or follows diphtheria, the combination being a very deadly one. The diphtheria bacilli are always associated with other organisms, chiefly the streptococcus. Laryngeal involvement is rare, and

death usually results from broncho-pneumonia. The lymphatic glands are markedly affected; the local symptoms are acute; the membrane is discoloured, foetid; the mucous membrane is deeply involved; and middle ear disease, gangrene of the jaw and septicaemia are common complications. The eruption of measles may assume an haemorrhagic or septic tendency.

2. Scarlet Fever. - Scarlet fever occurring with diphtheria will produce symptoms of a severe streptococcus infection superadded to those of diphtheria. The false membrane is usually discoloured and putrid; the glands of the neck are greatly enlarged and may suppurate; prostration is great; and there is usually high fever and vomiting. Death is frequent and usually occurs from septicaemia.

3. Whooping Cough. - Pertussis ~~eas~~ is one of the rarest complications of diphtheria, and is dangerous in that the diphtheritic process tends to invade the larynx, trachea, and lungs.

4. Typhoid Fever. - Diphtheria patients attacked by typhoid fever, or vice-versa, cannot hardly be expected to recover, death occurring from septicaemia or broncho-pneumonia.

5. Chicken-Pox. - This is a rare complication of diphtheria, and unless it be of the gangrenous variety does not materially influence the prognosis.

6. Rubella. - German measles has only in very

exceptional instances been observed to complicate diphtheria.

7. Tuberculosis. - Diphtheria has always an unfavourable effect upon tuberculosis hastening a fatal termination, or lighting up the malady when engrafted upon it. Furthermore, the presence of tuberculosis makes antitoxin badly borne.

8. Combinations. - That of measles and scarlet fever with diphtheria is commonest, though almost any other may occur.

RECRUDESCENCES AN RELAPSES.

Recurrences of diphtheria are not infrequent, and are observed in persons apparently predisposed to them. Relapses are much more uncommon, but quite possible as the bacilli continue to thrive in the patients' throat a long time after the subsidence of the attack, which, again, confers only a temporary immunity.

DIGESTIVE SYSTEM.

In mild cases of diphtheria digestive troubles are but seldom observed. The occurrence of vomiting and anorexia in severe cases have already been noted. When complicated with toxaemia the disease may be accompanied by profuse diarrhoea or even haemorrhage from the bowels. Extension of the exudative process to the oesophagus or stomach may be observed.

URINE.

The quantity of urine passed in ordinary cases of diphtheria is much as normal. It may, however, be diminished, or, in severe cases, suppressed.

Albuminuria. - The presence of albumin in the urine is regarded by some as a constant symptom (not a complication) of the disease and as being of a diagnostic importance equal almost to that of a bacteriologic examination. Generally speaking, however, it may be said to occur only in about from one-third to two-thirds of the cases, one the average in one-half. It is met with in both mild and severe cases, and in an amount in direct proportion to the severity of the local and general symptoms. It therefore allows of considerable diagmostic interpretation. Usually, however, the quantity of albumin found is not great, though it has sometimes been observed to the extent of 20 grams to the litre. As a rule albuninuria does not persist beyond ten days, though it has been sometimes seen to last beyond that period and to be of a more or less intermittent character. It has been observed to occur even as early as the first or second day of the disease, or, on the other hand, not until several weeks after the patient's recovery. It is due to toxaemia, not to direct infection of the kidney by the bacilli. It appears, moreover, to be much less common in the benign form of diphtheria than in any others. Councilman, Mallory, and Pearce (loc. cit.) regard the albuminuria of diphtheria as being due to

an acute renal degeneration of an intensity varying with the toxicity of the bacilli. When interstitial and glomercular changes complicate diphtheria - which is common in older children and in cases prolonged - it is not usually accompanied by oedema or anasarca.

BLOOD.

The Red Corpuscles. - In cases of diphtheria accompanied by high fever the concentration of the blood is marked. This is believed to be due to a lymphogogic action of the diphtheria toxin producing an increase in the specific gravity of the blood. Cuffer (Rev. mens. de Med., 1878, p. 519) found a great increase of the red cells, 7.2 - 7.8 millions on three occasions, and others, as Morse (Boston Med. Surg. Jour., vol. 132, p. 228) and Billings (Johns Hopkins Bull., 1894, p. 105; New York Med. Rec., vol. XLIX, p. 577), have reported abnormally high proportions, e.g., 5.1 - 5.6 millions during the first week. Morse, again, has once found as high numbers as 6.8 millions. In a few cases slight anaemia has been observed with the fall of temperature and in these the red cells may show some slight morphological change in the way of polychromasia and the usual deficiency of Hb. Engel (Deut. med. Woch., 1897, pp. 118, 1377; XV. Congr. f. inn. Med.) reports the finding of nucleated red cells. The slight diminution of Hb. may become great where many red cells have been lost. In patients not submitting to

the antitoxin Billings (loc. cit.) found an average loss of 10 per cent.

The Lencocytes.- That lencocytosis occurs to a greater or less extent in all cases of diphtheria is an established fact. It varies according to the severity of the disease. The myelocytes and lymphocytes are usually markedly increased in diphtheria so that the blood may become almost lenkemic. The lencocytosis of diphtheria begins very early when the disease develops suddenly, and reaches its acme within one or two days, or begins more slowly and increases steadily for several days, or until death. The height of the lencocytosis is usually considerable, 25,000 to 30,000 cells being frequently seen in severe cases, the majority of patients dying showing from 25,000 to 50,000, so that a high and progressive lencocytosis is of grave omen. Mild attacks, however, especially in adults, may show no increase. Hyperlencocytosis has sometimes been observed by several, notably by Felsenthal (Arch. f. Kinderh., Bd. 15, p. 78) who, in an agonal case, counted 148,000. The degree of lencocytosis appears to be proportional to the extent and depth of the pseudomembrane, and to be little affected by the height of the fever.

In cases of well-marked lencocytosis the polynuclear neutrophile cells are usually observed to be increased in both numbers and proportions; and lymphocytes are relatively more abundant. Eosinophile cells are, however, usually reduced in

proportions, often remain in low normal ratio, and sometimes appear to be entirely absent. According to Engel (loc. cit.), myelocytes, both neutrophile and eosinophile, are frequently found in the blood of diphtheria patients, and when these cells form over 2 per cent., the prognosis is very unfavourable. The number of myelocytes will usually be found to vary from day to day, and certain fatal cases may show them to be absent from the blood altogether.

The lencoytes during an attack of diphtheria frequently show marked degenerative changes; and in all severe infections the lencocyte-shadows are seen and may become very numerous in fatal cases (Klein) Baumgarten's Jahr., 1894, p. 266; Volkmann's Vortr., 1893, No. 87). Deficiency of chromatin and of neutrophile granules may be observed in connection with many of the cells, principally the polynuclear forms, even before they have become fragmented. This change in the staining capacity of the lencocytes may be made of value in prognosis, for it indicates cellular degeneration (Gabritschewsky - Ann. de l'Inst. Pasteur, 1894, p. 673). File (Lo Sperimentale, 1896, p. 284) regards these pale staining cells as essentially necrotic. In certain fatal cases an increased acidophile tendency of the neutrophile granules has been observed.

HEART.

Care must be taken not to confuse symptoms

occasioned by organic lesions of the heart and those due to ~~the~~ action of the diphtheria toxins upon the nerve-centres controlling it. The latter may be held responsible for many cases of heart paralysis.

In 800 cases of diphtheria Hibbard ("Heart Complications in Diphtheria" - Med. and Surg. Reports, Boston City Hospital, 1898) found irregular cardiac action 70 times. In 35 of these there were other cardiac disturbances, as murmurs and reduplication of the second sound. In 10 per cent. of all diphtheria cases the same author maintains that the latter phenomenon and an apical murmur are invariably present; and he regards them as usually due to relative mitral insufficiency, from insufficient contraction and dilatation, the latter caused by nervous changes in the heart and alterations in the myocardium: very rarely may an endocarditis be started by the action of the diphtheria bacillus. Hibbard weighed 11 hearts and found them to be heavier than usual by 37 grams. Thrombi were found in four, and degeneration of the pneumogastric nerve in all cases .22 of the patients had died from heart failure in three weeks, from which Hibbard concludes that if heart symptoms fail to appear after four weeks of convalescence the patient may be regarded as safe from cardiac complication. Endocarditis, myocarditis, waxy degeneration, thrombosis, dilation, and the other conditions described in the anatomic section, have all been reported as complicating diphtheria.

NERVOUS SYSTEM.

During a typical attack of diphtheria the nervous system is not usually affected. In severe and toxic cases, however, matters may be different and delirium, stupour, somnolence, apathy, convulsions, or tetanic spasms, be observed.

PARALYSIS.

Paralysis is due to the action of the toxin and is direct proportion to its amount.

Frequency. - The frequency of diphtheritic paralysis is not easy to estimate as so many cases occur when discharged from treatment. Woolacott ("Post - Diphtheritic Paralysis" - Lancet, 1900, II, 1482) has analysed 829 cases appearing in the report, for 1898, of the Metropolitan Asylums Board, and in order to ascertain whether paralysis is more common in severe than in mild cases, divides them into three classes as follows:-

Nature of Case.	Total.	Paralysis.	Percentage.	Severe Paralysis.	Death from Paralysis.
Severe...	223	64	28.6	19	5
Moderate.	566	75	13.2	7	1
Mild.....	40	..	..	..	..

Age of Occurrence. -

Diphtheritic paralysis usually occurs from the fourth to the twelfth day of convalescence, occasionally early in the disease, rarely after a month. Meyers ("Some Points about Post-diphtheritic Paralysis," Lancet, 1900, II, 869-871) has investigated 1316 cases of diphtheria and found 275 cases of post-diphtheritic paralysis (about 1 in 5) with 80 deaths. According to age, they were as follows:-

Age.	Number of Cases.
Under 5 years	104
5 to 10 ,,	138
Above 10 ,,	33

Sex. -

The majority of cases recorded above occurred amongst males.

Paralysis of the Palate. -

This occurs usually early in the disease, in severe cases only, and affects the velum palati. The condition has been termed "Diphtherische Frühlähmung" by Baginsky ("Diphtherie u. diphtheritischer Kroup" - Noth. Path., Wien, 1898); and in it swallowing is difficult, fluids come through the nose, the speech is nasal, and food may pass down the trachea and induce fatal pneumonia. The paralysis is nearly always total: a few unilateral cases have been occasionally observed. Baginsky considers these cases to be due to the involvement of the muscles of the velum by the false membrane, an acute myositis being induced.

Distribution of Diphtheritic Paralysis. -

Mayers (loc. cit.) gives the following findings:-

Locality.	Number of Cases.
Palate alone (40 per cent. of total paralysis)	110
Palate and ciliary muscles	5
,, ,, external rectus	27
,, ,, ocular muscle	3
,, ,, right facial muscle	1
,, ,, ciliary muscles and pupils	1
,, ,, larynx	1
,, ,, diaphragm	17
Total palate	166

VARIETIES OF PARALYSIS.

There are two varieties of post-diphtheritic paralysis - the benign or circumscribed, and the general or severe.

I. Benign, or Circumscribed, PARALYSIS. -

The majority of cases of post-diphtheritic paralysis are of this form which most often attacks the velum palati and pharynx. The condition is attended by difficulty in swallowing, regurgitation of fluids through the nose, laryngeal cough, and, in the case of children, inability to swallow except when the head is in the retracted position. The child finds it difficult to phonate, except in a nasal tone, and snores loudly during sleep. The velum will be found to have lost its mobility and

reflexes and to be anaesthetic. Similar signs are observed when the pharynx is involved. Inspiration of food may cause death by choking, or the same may occur from aspiration pneumonia. The duration of the malady averages two weeks.

II. GENERAL, OR SEVERE, PARALYSIS. -

This form is frequently an advancement upon the foregoing, but have the special tendency to affect the pharyngeal, laryngeal and ocular muscles. The patellar reflexes will be observed to be abolished or diminished almost from the outset. Occasionally, however, the patellar reflex may be seen to be slightly increased, and ankle clonus present, prior to the commencement of the paralysis. The latter may be observed in muscles of the feet, and formication, numbness, or complete amaesthesia may be complained of. Progression is effected in a shuffling manner. In severe cases the affected muscles may sometimes undergo atrophy; and at times, likewise, the symptoms may partake of an ataxic character, - the so-called "diphtheritic pseudo-tobes," - or, again, the paralysis may be absolute. As a rule the muscles of the upper extremities are less severely effected than those of the lower, but the loss of power in the arms has been known to be complete. The patient may, through paralysis of the muscles of the face and neck, be unable to support the head. Involvement of the muscles of the tongue likewise contributes to an idiotic expression, the

lips being relaxed and saliva pouring from them. The process may extend to many groups of muscles so that the child lies in a helpless heap in bed, breathing by the diaphragm alone.

DIAPHRAGMATIC PARALYSIS.

Paralysis of the diaphragm is always a very serious condition. The respirations are of a panting and rapid character; and the abdomen bulges during expiration and retracts on inspiration. Sudden death in these cases is common and from slight causes. Meyers (loc. cit),in the 1316 cases referred to, found diaphragmatic paralysis 21 times - 7.6 per cent. of all forms of paralysis - death occurring in 11, = 13.7 % from all forms of paralysis, in from six to seven days. In no case did the condition occur without being preceded or followed by some other form of paralysis.

CARDIAC OR VAGUS PARALYSIS.

Apart f rom cardiac disturbances being so often due to myocardial changes, it cannot be denied that in others the vagus nerve is responsible for the phenonena observed. According to Meyers (loc. cit.), 64 of the 80 deaths from forms of paralysis were due to involvement of the cardiac nerves; most of the cases wefe between two and nine years of age; the symptoms of the condition

appeared usually on the seventh day: earliest in the second: latest on the thirty-sixth; the average duration of life thereafter was four days; the cervical glands were greatly enlarged in many; and the temperature was most often subnormal. The symptoms observed in the circulatory system were:- Dilated heart; weak, irregular intermittent, or rapid action; heart sounds approximated; first sound faint, short, with systolic murmur, or heard reduplicated over the mitral and tricuspid areas; gallop thythm, brachycardiac, and heard with systolic murmurs. Nose-bleeding was sometimes observed; and sometimes collapse and sudden death took place. The temperature was first elevated and then subnormal; the respiration laboured and occasionally sighing. Oedema of the lungs was somewhat common and albuminuria seldom absent. Occasionally there was haematuria, anuria, convulsions, drowsiness, restlessness and delirium.

Cardiac paralysis may be either a late or early symptom during the progressive form of general paralysis, but it has been seen to occur alone. When mild there will be attacks of fainting, dyspnoea, and inequality in the pulse, which are usually soon recovered from, though recurrence with sudden death may be observed. In the more severe form of the malady, however, it is often ushered in by vomiting, nausea, and abdominal pains, superadded to which may be precordial oppression. The breathing gradually becomes laboured and more

difficult; and the pulse is usually accelerated. The patient is very anxious and restless, but may however remain apathetic. Such cases not unfrequently recover, but often the patients die either suddenly during a dyspnoea attack or sudden movement, or from a rapid progression of the disease. The Electrical reactions are found to vary so much that they are of little aid either for diagnosis or prognosis.

AFFECTIONS OF THE SKIN.

Erythema. This appears to be by far the most common skin lesion, is accompanied by a slight rise in temperature, occurs at any stage of the disease, and on any part of the body. It lasts about four days and leaves a brownish discolouration wherever located.

A measly eruption; in the certain absence ofmeasles, has been occasionally observed.

A Scarlatiniform rash may occur in severe cases of the disease, and is apt to suggest the presence of Scarlatina itself.

Haemorrhagic eruption may be noted in septic cases.

Erysipelas and measles are somewhat common complications of diphtheria; rare ones are;- Raynaud's disease, pyaemic and abscesses.

AFFECTIONS OF THE JOINTS.

It is quite exceptional to find a case of diphtheria complicated with joint-disease. The condition is usually only seen after the subsidence of the disease or during convalescence, and affecting the knee and wrist. The Arthrites in children may be simple or suppurative, the

first being due to the toxic action of the diphtheria bacilli, the latter to pyogenic organisms, the same being productive of a high mortality. .

BRONCHO-PNEUMONIA.

Broncho-pneumonia is the most serious pulmonary complication of diphtheria; is not produced, as a rule, by the klebs-Löffler bacillus, but by the streptococcus or pneumococcus; and usually terminates laryngeal cases that have been operated upon. It occurs very often in institutions, and in frequency seems to vary with the season of the year and the treatment adopted. The symptoms are of the ordinary kind and as if no diphtheria were present. The complication appears at any stage. or after the disappearance of the membrane The mortality from it is very high indeed.

Bronchitis.

Laryngeal cases are frequently complicated by bronchitis, which latter is very apt to develop into pneumonia. With its onset the temperature becomes elevated; and the symptoms are of the ordinary kind.

EMPYEMA.

Empyema is most apt to occur in septic cases.

PLEURISY.

Pleurisy is much more common than empyema.

Pulmonary Abscess.

Abscess of the lung occasionally occurs.

LOBAR PNEUMONIA.

As a direct complication of diphtheria lobar pneumonia is very rare, not so, however, broncho-

pneumonia distributed over a lobe.

DIAGNOSIS.

CLINICAL DIAGNOSIS.

The clinical diagnosis of diphtheria is often a matter of considerable difficulty but the recognition of the ordinary pharyngeal form of the disease should not be so if an epidemic be prevailing. The presence of the false membrane and the occurrence of albuminuria should receive particular consideration. The only certain evidence of the disease, however is the finding of the Klebs-Löffler bacillus in the former. A knowledge of the local and general manifestations will often allow of a correct diagnosis and may be the only means available in country practice, but should invariably be confirmed by laboratory methods: in out-of-the-way places this can be done by posting a scraping of the membrane to one of the institutions which specially cater for such cases.

The following are the conditions which may have to be differentiated from diphtheria:-

1. Pharyngeal Catarrh.-

As this is often the beginning of diphtheria, development must either be awaited or a culture taken. In the former case should the membrane not appear

after the lapse of 24 hours, diphtheria may be excluded.

2. Thrush.-

In thrush the lesions are less often than in diphtheria seen on the pharynx, uvula, and palate; but are usually located on the lips and tongue, and occur as sticky white flakes in appearance like curdled milk.

3. Quinsy.-

In quinsy or tonsillar abscess pain is a very prominent symptom, and may be referred to one or both ears according as one or both tonsils are involved. The latter will be found to be greatly enlarged, of a deep red colour, firm, and oedematous, while the pillars of the fances, arches, and uvula are manifestly congested. In severe cases the tonsils may meet in the median line, from distension by abscess, and so push the uvula forwards. It may be difficult even to open the mouth owing to fixation of the jaw. The fact of instant relief being afforded by breaking of the abscess or incision is very suggestive and soon leads to the disappearance of any suspicions. exudate present, failing which the latter shows no disposition to spread. A culture should invariably be taken.

4. Follicular Tonsillitis.-

The important points of differentiation between this disease and diphtheria may be tabulated thus:-

Follicular Tonsillitis.	Diphtheria.
iate soft, pultaceous, yellowish-	1. A tough, ashy-gray, continuous and uniform false - membrane covers the tonsils.
te occurring in spots or patches uated over the mouth of the fol- les with areas of redness inter- ing.	
exudate is easily removed leav- a smooth surface.	2. The exudate is very adherent, and can be torn off in strips only, leaving a bleeding erosion.
deposit is limited to the tonsils portant.)	3. The pillars of the fauces and uvula are involved as well.
n creamy deposits form a contin- s layer, removal is either not llowed by re-formation, or very late	4. Removal of membrane is followed by re-formation within 12 to 24 hours
h temperature when present lasts y for a day or two.	5. Persistent elevation of temperature often observed. Albuminaria common.
uminuria extremely rare.	
rvical lymphatic glands seldom llen, or only slightly.	6. Cervical lymphatic glands usually markedly swollen.
plications rare and mild.	7. Complications frequent and serious.
teriologic examination shows no ecial organism; often, however, reptococci and Staphylococci.	8. Bacteriologic examination shows the Klebs-Löffler bacillus.

5. Pseudo - Diphtheria.-

In pseudo-diphtheria - caused by germs other than the Klebs-Löffler bacillus, as the streptococcus pyogenes staphylococcus, pneumococcus, colon bacillus, and occurring sometimes primarily, but more often in association with exanthematous diseases, especially scarlet fever - the temperature is higher than in true diphtheria prostration is less; the pulse is not so weak; and the patient neither looks nor feels so ill. In pseudo-diphtheria, moreover, the membrane shows less tendency to involve neighbouring parts, is less adherent and does not leave such a bleeding surface when detached; the disease is of shorter duration; albuminuria is less common; and paralysis never follows.

6. Scarlet Fever.-

In certain cases of diphtheria there may be an erythema, but the rash is darker, generally confined to the trunk, and disappears earlier. The onset is less abrupt; there is usually a more marked degree of prostration, and a culture from the throat reveals the Klebs-Löffler bacillus. The possibility of the co-existence of the two diseases should be remembered.

7. Measles.-

The angina observed in measles can usually be recognised as such by giving due weight to other symptoms, as catarrh, Koplik's spots, and the cutaneous lesion.

8. Acute Affections of the Larynx.-

Differentiation of these can often only be determined by a bacteriologic examination.

9. Typhoid Fever.-

Inflamation of the pharynx and larynx may be observed in typhoid fever but the concomitant symptoms of the latter will indicate its parent.

10. Small - Pox,-

The same remarks apply here as in typhoid fever. The occurrence of other cases in the locality will be specially suggestive.

11. Syphilis.-

The history of the case will usually determine this disease. A bacteriologic examination will clear up any doubts remaining.

12. Other Lesions.-

Herpes and other affections with lesions at first sight like that of diphtheria can be recognised similarly. The history of the case, epidemic prevailing and bacteriologic experimentation, are of Special importance.

BACTERIOLOGIC DIAGNOSIS

(A.) The Direct Method.-

In cases where an immediate diagnosis is required the false membrane may be subjected to direct examination The method however is not, as a rule, satisfactory. A portion of the exudate is removed by means of forceps or swab and smeared upon a cover glass or glass side, passed through a spirit flame to fix, stained with Löffler's methylene-blue solution, and examined. Often no Klebs-Löffler bacilli will be found (though perhaps subsequently demonstrated by the culture method) and other organisims present are apt to be mistaken for them.

(B.) The Indirect, or Culture, method.-

A sterile platinum wire with a small loop at the end, or a cotton - covered swab, is introduced into the throat so as to rest for a moment upon the false membrane, after which it is carefully smeared over the surface of at least three of Löffler's blood serum mixture tubes; which, thus inoculated are deposited in an incubator at a temperature of 37°c. for 12 hours, and then examined. If Klebs-Löffler's bacillus be present, a smeary yellowish- white layer will be present upon the first tube, a similar layer with outlying colonies on the second tube, while the third tube will show rather large, isolated, whitish or slightly yellowish, smooth colonies, which, again, may be china-

-white in appearance. Under the microscope these colonies being found to consist of true diphtheria bacilli, will confirm the diagnosis of the disease, and will, at the same time, give pure cultures of the bacillus when transplanted. A rapid method, suggested by Concetti ("Rasche Methode zur bakt. Diagnose der Diph.,"- Wien Med. Woch., 1900,S. 462,463,) is that of taking a sterile cotton swab, which is then impregnated with glucose, glycerinated ager-ager, the culture taken as described and placed in a glass tube, plugged and kept at a temperature of 970 to 99°F. in the thermostat for 4 to 6 hours; The diphtheria bacilli can be stained with Neisser's solution and recognised before any other organisms present have had time to develop.

PROGNOSIS.

Age of the Patient.-

That the age of the patient is of considerable importance as regards prognosis will be seen from the following table based upon an observation of 2093 cases which occurred at the Boston City Hospital in 1900 and 1901 (Burrows - "Clinical Study of 2093 cases of Diphtheria" Amer. jour. Med. Sci., 1901, CXXI, 135-151):-

Age of the Patient.	Deaths.	per cent
0 - 1 Years	4.0	" "
1 - 2 Years	33.0	" "
2 - 3 "	23.0	" "
4 - 5 "	15.6	" "
5 - 6 "	14.6	" "
7 - 8 "	10.4	" "
8 - 9 "	8.6	" "
9 - 10 "	2.08	" "

Again:-

Under 5 Years	Death occurred	in	21.3	per	cent
From 5 -10 "	"	"	8.40	"	"
" 10-15 "	"	"	3.10	"	"

The following tables represent the mortality according to age in the Asylum's Board Hospitals: Table I from 1888 - 94 (11,598 cases), and Table II . from 1892 - 93.

Table I.

Males.		Females		Total.		Per Centage.		
						Males	Females	Total.
Admitted.	Died.	Admitted.	Died.	Admitted.	Died.			
5245	1677	6 353	1839	11,598	3576	32.0	29.0	30.3

Table II.

Ages		Males		Females		Total.		Percentage.		
		Admitted.	Died.	Admitted.	Died.	Admitted.	Died.	M.	F.	Total
Under 1,	1892	28	14	21	17	49	31			
	1893	18	15	22	22	40	37			
		46	29	43	39	89	68	60.44	90.69	76.4
1 to 2,	1892	54	40	54	26	108	66			
	1893	88	55	78	51	166	106			
		142	95	132	77	274	172	66.9	58.3	62.7
2 to 3,	1892	77	45	86	45	163	90			
	1893	117	73	102	58	219	131			
		194	118	188	103	382	221	60.82	56.28	57.8
3 to 4,	1892,	94	48	101	48	195	96			
	1893	158	90	138	59	296	149			
		252	138	239	107	491	245	54.76	44.76	49.9
4 to 5,	1892	101	39	138	67	240	106			
	1893	154	61	185	82	339	143			
		255	100	324	149	579	249	39.2	45.97	43.0
5 to 10	1892	301	74	330	89	631	163			
	1893	403	114	477	119	880	233			
		704	188	807	208	1511	396	26.7	25.72	26 .2
10 to 15	1892	84	8	125	7	209	15			
	1893	135	18	163	12	298	30			
		229	26	288	19	507	45	11.35	6.59	8.8
Over 15	1892	150	6	264	10	414	16			
	1893	241	18	369	18	610	36			
		391	24	633	28	1024	52	6 .13	4.42	5.0

GRAND TOTAL

Males		Females		Total		Per Centage		
						Males	Females	Total.
Admitted.	Died.	Admitted	Died	Admitted	Died			
2213	718	26 54	730	4857	1448	32.44	27.0	29.8

Site of the False Membrane.-

Cases with the membrane in the larynx show the highest mortality; the prognosis will, however, varying according to the nature of the treatment adopted - intubation, tracheotomy, antitoxin, and so forth. The following table gives an idea as to death-rate according to location of the membrane:-

ANALYSIS OF 1000 CASES OF DIPHTHERIA

Site of membrane,	Total Number of cases	Deaths	per centage
Fancial (alone).	666	81	12
Laryngeal (Alone).	4	1	25
Nasal (Alone).	2	1	50
Faucial and Laryngeal	112	51	43.7
Faucial and nasal.	165	106	64.2
Faucial, laryngeal and nasal	49	30	61.2
Membrane involving the buccal cavity and lips	6	2	33.3
Membrane involving the hard palate.	12	11	91.6

Surroundings.-

That diphtheria is a much more fatal disease in institutions than elsewhere is a fact well known, and due probably to the frequency of broncho-pneumonia therein

When actually epidemic the disease attacks all members of the community equally apart from surroundings and sanitary conditions, and is sometimes remarkable in that it , amongst the upper classes it runs a more mal-

ignant and fatal course than amongst the poor, due probably to the receptivity of the "Soil" in the former class of patients, who, again, recover from sequelae more quickly once the acuteness of an attack has passed .

Season.-

A fact of importance often overlooked in prognostication is the influence of the season of the year upon diphtheria, which seems to be more dangerous in the cold wintry months. The following table speaks for itself:-

MORTALITY FOR JANUARY AND APRIL, 1900, IN THE HOSPITALS OF THE METROPOLITAN ASYLUMS BOARD LONDON.

Month	Number of cases admitted	Mortality.
January.	785	16.73 per cent
April.	530	8.17 " "

In the same institutions, from 1888 to 1900, the maximum mortality occurred in January, and the minimum in April.

Treatment Adopted.-

The reduction of the death-rate of diphtheria by antitoxin will be referred to when dealing with that method in the next chapter.

Tracheotomy versus Intubation.-

The following totals, from Biggs and Guerard's compilations shows that the mortality favours intubation as the operation of election:-

Tracteotomy		Intubation	
Number of cases	Mortality	Number of cases	Mortality
1355	42 per cent	1173	30.8 per cent.

The Value of Early treatment is clearly demonstrated in the followong statistics by the same authors:-

Commencement of treatment	Cases.	Deaths.	Percentage Mortality.
IST. day of the disease	1415	5	3.5
2nd. " " " "	2640	213	8.0
3rd. " " " "	2340	300	12.8
4th. " " " "	1458	346	23.6
5th. " "and"after."	1912	671	35.0

TREATMENT.

PROPHYLAXIS.

The New York City Health Department makes the following judicious recommendations with reference to the prevention of diphtheria: being clear, concise, and covering the entire question, they may with advantage be cited at this juncture.

"If possible one attendant should take entire care of the sick person, and no one else besides the physician should be allowed to enter, the sick-room. The attendant should have no communication with the rest of the family. The members of the family should not receive or make visits during the illness.

"The discharges from the nose and throat must be received on handkerchiefs or cloths, which should be at once immersed in a carbolic solution (made by dissolving six ounces of pure carbolic acid in one gallon of hot water, which may be diluted with an equal quantity of water). All handkerchiefs, cloths, towels, napkins, bed-linen, personal clothing, night-clothing, etc., that have come in contact in any way with the sick person, after use should be immediately immersed, without removal from the room in the above solution. These should be soaked for two or three hours, and then boiled in water or soap-suds for one hour.

"In diphtheria and scarlet fever great care should be taken, in making applications to the throat and nose, that the discharges from them in the act of coughing are not thrown into the face or clothing of the person making the applications, as in this way the disease is likely to be caught.

"The hands of the attendant should always be thoroughly disinfected by washing in the carbolic solution, and then in soapsuds, after making application to the throat or nose, and before eating.

"Surfaces of any kind soiled by the discharges should be immediately flooded with the carbolic solution

"Plates, cups, glasses, knives, forks, spoons, etc. used by the sick person for eating and drinking must be kept for his especial use, and under no circumstances removed from the room or mixed with similar utensils used by others, but must be washed in the room in the carbolic solution and then in soapsuds. After use, the hot soapsuds should be thrown into the water-closet and the vessel which contained it should be washed in the carbolic solution.

"The room occupied by the sick person should be throughly aired several times daily, and swept frequently, after scattering wet newspapers, sawdust, or tea-leaves on the floor to prevent the dust from rising. After sweeping, the dust upon the woodwork and furniture should be removed with damp cloths. The sweepings should be burnt and the cloths soaked in the carbolic solution.

In cold weather the sick person should be protected from draughts of air by a sheet or blankets thrown over his bed while the room is being aired.

"When the contagious nature of the disease is recognised within a short time after the beginning of the illness, after the approval of the Health Department Inspector, it is advised that all articles of furniture not necessary for immediate use in the care of the sick person, especially upholstered furniture, carpets, and curtains, should be removed from the sick-room.

"When the patient has recovered, the entire body should be bathed and the hair washed with hot soapsuds, and the patient should be dressed in clean clothes ((which have not been in the room during the sickness) and removed from the room. Then the Health Department should be immediately notified, and disinfectors will be sent to disinfect the room, bedding, clothing, etc., and under no conditions should it be again entered or occupied until it has been throughly disinfected. Nothing used in the room during the sickness should be removed until this has been done."

The disinfecting of rooms occupied by diphtheria patients to be effected should be as through as possible Thus, the walls and ceilings should be rubbed down with bread, or washed with 1: 1000 perchloride of mercury solution, and the woodwork, furniture, and floor ought to be scraped and treated with the same solution.

The walls might with advantage be repapered or repainted; and carpets. mattresses, upholstery, etc., should be disinfected by steam, books, toys, etc., being burnt. Formaldehyde Vapour, whilst not being destructive to furniture or delicate articles, and possessed of germicidal powers, is quite useless for penetrating upholstery, bedding, etc. The vapour may be obtained by burning formalin candles, doors and windows being plugged tightly, drawers closets. etc., opened widely, and articles to be fumigated spread out as much as possible during its use.

As to the duration of the patients isolation. this should last as long after the apparent disappearance of the disease as cultures of the diphtheria bacillus (upon the persistence of which antitoxin seems to have little or no influence) can be obtained from the mucons membrane. Walsh ("Clinical Relations ot the Löffler Bacillus - "New York Med, Jour., 1898. LXVII, 858), examining 2500 cultures from 800 convalescents, found the bacillus absent as early as the sixth day and present as late as the eighth week. Parks and Beebe in 2566 cultures from 605 convalescents found the bacillus absent

In 3days after the disappearance of the exudate in 304 cases

" 7 " " " " " " " " 176 "

" 12 " " " " " " " " 64 "

" 15 " " " " " " " " 35 "

" 21 " " " " " " " " 12 "

" 28 " " " " " " " " 4 "

" 63 " " " " " " " " 2 "

A point in the prophylactic treatment of diphtheria which is a t to be lost sight of is the uncertain period of convalescence. It frequently happens - as has been already noted - that long after all membrane has disappeared active bacilli may persist in the throat, often for as long as six months, or longer in deeply fissured tonsils, The disease may be communicated by such throats in the act of kissing young children or adults with sensitive throats or with a broken mucous membrane of the mouth; for which reason the indiscriminate kissing of young children on the lips should be wherever possible prohibited.

PROPHYLAXIS BY ANTITOXIN.

The value of antitoxin as a means of protecting individuals against diphtheria is daily becoming more apparent, and the remedy should be adopted by all who have come in contact with diphtheria patients and by others as a precautionary procedure whilst within reach of the disease. The literature amply testifies to the efficacy of antitoxin as a prophylactic. Mus. Biggs (Jour. Amer. Med. Assoc., Mar. 17, 1900, p. 695) states that of the 3,000 diphtheria "contacts" who in New York, received a prophylactic small dose 150 units of antitoxin, only 9 contracted the disease and then only in a mild form. At the New York Infant Asylum, before immunization was practised 107 cases occurred in 108 days, but after the introduction of antitoxin only 5 cases in 112 days. According to Coues ("Results of Immunizing Fifty children at St. Mary's Infant Asylum " - Boston Med. and Surg. Jour., 1898, CXXXIX, 36) from February 15th. To March 22nd. 1898 there were 18 cases of diphtheria. but for three weeks after the latter date, when antitoxin was begun no cases occurred for three weeks. Krauss ("Ueber die Prophylactisch Immunisirung kranken kinder gegen Diphtherie" - Prag. Med. Woch., 1900, XXV, 217 - 220, 230 - 233) of 122 immunized cases observed in hospital, 44 were scarlet fever, 2 of which latter contracted diphtheria; 31 cases of children who were sent to the diphtheria pavilion and found not to have true diphtheria;- no cases contracted it; 47 measles cases, many of them complicated - one developed diphtheria.

Hence of these 122 cases, all of whom were more or less exposed to the disease and all ill with diseases

Place of Observance	Children Immunized	Cases of Diphtheria developing among Those Immunized Between 1 and 30 days.	Cases Developing within 24 Hours.	Cases Developing after 30 days.	Number of cass. of Diphtheria that Occurred in the Institutions Previous to Immunization.
Nursery and childs Hospital	136	0	0	0	46 cases in 90 days; 15 cases in 18 days;
New York Juvenile Asylum.	81	0	0	0	12 cases; 3 cases in 2 days.
New York Catholic Protectory	114	0	1	0	5 cases in 3 days.
Bellevue Hospital.	11	0	0	0	
Health Department Inspectors	232	1 mild on the 19th. day	3	one 30th. 3 one 31stor one 55th.	3 cases in 10 days One or more cases in more than 90 families.

likely to be complicated by diphtheria, only 3 became infected: on the twenty-sixth, twenty-seventh, and forty-first day after inoculation. The dose of antitoxin ranged from 200 to 400 units, the latter being given to the children with suspected diphtheria.

The following table (Biggs - loc. cit.) will show the results at other institutions of New York City;-

In New York City the Department of Health have endeavoured to impress upon all practising physicians t the desirability of immunizing patients, for the prevtion of diphtheria in the following circular:-

"A CIRCULAR TO PHYSICIANS SETTING FORTH THE IMPORTANCE OF IMMUNISATION FOR THE PREVENTION OF DIPHTHERIA.

"From January 1, 1895, to January 1, 1900, immunising injections of antitoxin were administered to 6,806 individuals by the Inspectors of the Department of Health. Of these individuals 18 contracted diphtheria of a mild type; one case only, of diphtheria complicated with Scarlet fever, terminated fatally. It is probable that in these 19 cases an insufficient amount of antitoxin was used to produce immunisation.

"The records of the Division of Bacteriology show that from January 1, 1898, to January 1, 1900, 682 cases of diphtheria occurred which were secondary to an original case in the same family. Under "Secondary" are included only those cases which occurred at least twenty - four hours after and within thirty days of the primary case. Of these 682 cases, 61 died a mortality of 8.9 per cent. Had these 682 individuals received antitoxin when the physician first visited the family, probably not one of them would have contracted the disease. The above figures represent only a fraction of such secondary cases occurring in New York City during 1899.

"The Board of Health strongly advocates antitoxin immunisation in diphtheria. Physicians are especially urged to immunize every child under their care who has been exposed to the infection from a case of diphtheria.

If this be done, it is believed that the number of cases of diphtheria occurring in the city will greatly diminish. To this end the department of Health offers to furnish antitoxin for immunising purposes free of charge. When the physician so desires, the antitoxin will be administered by the Inspectors of the Department of Health.

The value of antitoxin has by the Health Department of Burton - on - Ttent, been impressed upon the medical profession off that place by means of a circular to the same effect.

The efficacy of the remedy is instanced by Porter (Lancet, 1901, I, p. 1753) in connection with an epidemic which occurred in the Chelmsford and Maldon district, where there were 24 families in which diphtheria had occurred. 144 members of the families remained unaffected, and to 136 of these prophylactic injections of diphtheria antitoxin were given, and among them a single doubtful case of diphtheria occurred, whilst of the 8 uninjected individuals 3 subsequently developed diphtheria. In another series of 24 families, no member of which was injected of 125 individuals, 21 subsequently developed diphtheria.

Blake (Lancet, 1901, I, p. 247) reports that in a convalescent home containing 38 children, three consecutive cases of diphtheria occurred. The remaining 35 children were each injected with antitoxin (334 units each), and no further case developed.

According to Cobbett (Jour. of Hygiene, I, No. 2, 1901, p. 228), a severe outbreak of diphtheria occurred in the districts of Cambridge and Chesterton in the autumn of 1900, but by means of prophylactic antitoxin injections the epidemic was soon stamped out.

Jump (Phila. Med. Jour., Jan. 11, 1902, p. 69) maintains that children, whilst being less susceptible to diphtheria, enjoy a larger artificial immunity to the disease: and it is his custom to isolate the sick child, to disinfect the rooms occupied, to remove the sufferer so soon as ever convenient, at the same time giving an immunising dose of antitoxin. The same author considers that (1) as diphtheria antitoxin is practically harmless, all exposed persons should receive an immunising dose in proportion to age; (2) that 250 units should be given to children under ~~the~~ two years and 500 to others; (3) that the immunity will last for at least three weeks, provided a reliable antitoxin be used; and (4) that all exposed persons should be removed from infected surroundings, either by thorough disinfection of their own quarters or by removal to other places. If this be impossible, the immunising doses should be repeated every third week.

For the purpose of prophylaxis at least 300 units should be given to children, and 500 units to adults: the latter is a dose to be recommended in all cases. The immunity resulting - usually in two or three hours, slowly passes off, and may be considered at an end in three weeks.

TREATMENT OF THE ATTACK.

HYGIENIC MEASURES%

For the reason that diphtheria bacilli grow well amidst damp and dark surroundings, the sick-room should be one that is freely exposed to both sunlight and fresh air, and, for obvious reasons, there should be no stationary lavatory or water-closet in the apartment. Whenever possible the patient should have the use of two rooms one opening into the other one of them to be used at night, the other by day, the unoccupied one to be properly disinfected and aired as at liberty. Even the mildest cases should be kept in bed throughout the attack; and the more severe ones during convalescence also; more especially should the patient have been suffering from Cardiac depression. A sponge-bath of tepid water, salt water, or of alcohol and water, will materially contribute to the patient's comfort.

DIET:- It is important that nurslings be kept away from the breast: they can, however, receive the breast-milk drawn by a suitable pump. The feedings should be effected with regularity, but be lighter in quality and quantity than in health owing to the gastric disturbances commonly accompanying diphtheria. One should confine the diet to milk, in the diluted form: peptonised in the case of young children. Feeding is apt to be difficult to effect in septic cases, owing to marked disinclination on the part of the child to be disturbed; the easily excited vomiting: and the dysphagia from

swelling and pain. It becomes ~~therefore~~, necessary, therefore, to administer the nourishment, so necessary in these cases, by means of the stomach tube and gavage appears to be even more satisfactory than rectal alimentation with children under three years. Elder children usually object to the tube through the mouth, but tolerate it through the nose; and gavage by this route, even in intubated cases, will be found extremely satisfactory, and allows of concentrated broths, meat-juice, and even raw eggs, being so administered.

THERAPEUTIC AGENTS OTHER THAN ANTITOXIN.-

ALCOHOL is now by all admitted to be the most convenient and powerful drug to offset the ravages of the disease on the nervous centres and for the control of the circulation. Stimulation by alcohol (in the form of whisky or brandy, in doses well diluted with water, beginning with from 10 to 15 drops three or four times a day for an infant up to an ounce or more for a child of three of four years) should be instituted as soon as the diagnosis is assured. Thus one may expect to be able to prevent the depressing effects of the diphtheria poison, the need for the measures of stimulation being indicated by the presence of marked prostration, feeble pulse and a weak first cardiac sound. As the child will usually object to taking both food and stimulants, they may be mixed together. An additional advantage especially in intubated cases of alcohol in small doses lies in the fact of its exciting and strengthening the

cough, thereby getting rid of laryngeal obstruction.

STRYCHNINE, next to alcohol, is the best stimulant. It is usually, however, given in too small doses to obtain its maximum benefit, care being taken to watch the deep reflexes for signs of poisoning. It may be administered, in tablet form or hypodermically, in doses of from $\frac{1}{100}$ of a grain, to a child of a year, every two or three hours, up to from $\frac{1}{50}$ to $\frac{1}{30}$ of a grain every six to eight hours, for a child of four years.

Digitalis, though indicated on theoretical grounds for the certain cardiac conditions of diphtheria has now lost much of its former popularity, in that, before its good influence upon the heart can be had, an unfavourable action upon the stomach is manifested; and the same can be said for ammonium carbonate and camphor. In cases of threatened cardiac paralysis occurring late in the disease nothing, according to Holt ("Diseases of Infancy and childhood," 1900) is so valuable as morphine employed hypodermically, the drug being given in full doses - according to age - and repeated every two hours, keeping the child under its influence for some days. The highly commended remedies of days prior to the introduction of the only specific - antitoxin - have now passed into disuse; and the fact of the more prominent ~~being~~ of them being below mentioned by no means implies an advocacy on the part of the writer.

Tincture of the perchloride of iron, (diluted

with water and glycerin) for long enjoyed a great popularity in cases of laryngeal and tonsillar diphtheria, but has the serious disadvantage of exciting vomiting and ~~if~~ of aggravating any gastric disorders present.

Perchloride of Mercury - in doses equal to $\frac{1}{6}$ to $\frac{1}{2}$ of a grain per day well diluted - has been much vaunted for the control of laryngeal diphtheria.

Subchloride of Mercury, or Calomel, is stated to have given satisfactory results in laryngeal cases, 15 grains of calomel being volatalized, under a canopy placed on the patient's bed, every two hours for two days and nights; then every three hours for the third day, every four hours for the fourth, and thereafter three times daily, according to the nature and progress of the case. Symptoms of mercurial poisoning were, however, frequently observed after its use, the attendant likewise suffering.

Pilocarpine has been much vaunted by Howe(Med. Brief., Aug., 1895) and others. Cohen (Phila. Polyclinic, No. 16, 157, 1896) states that guaiacol is an effective local germicide in diphtheria, and a prophylactic against the disease as well. A 10 per cent. solution of citric acid has been given internally as a "specific," and hyposulphite of soda with glycerine as a topical application.

Graetzr (Münch. med. Woch. p. 1164, 1896) strongly advocates tincture of myrrh. ~~di~~ internally; whilst Chlorine, similarly administered, has been vaunted by Meyers (New York med. Jour., LXVIII, 675, 1898) and others.

Local Treatment.

Nearly all the remedies in the pharmacopoeia have been used upon the lesion in the throat: numerous are the formulae for garles, swabs, paints, sprays and throat washes to be found in the literature, and most practitioners doubtless have their own favourite remedy or combination. The importance of local treatment has, however, since the introduction of antitoxin, been considerably minimized, though admitted. Peroxide of hydrogen - as a gargle or spray is usually considered to be the best oral application for pharyngeal or nasal diphtheria. For infants, who obviously cannot use a gargle, Norikove '(La Médicine, Oct. 8, 1902) recommends the peroxide to be given internally, thus: hydrogen peroxide, 5 to 7 c. c. : distilled water, 85 c. c.; syrupus simplex, 15 c. c. Used as a swab, the tincture of the perchloride of iron (with glycerine) is a valuable remedy. An important object of local treatment being to effect a through cleanliness of the affected part and thereby to prevent , if possible, absorption of the ptomaines, the procedure should have the medical attendant's painstaking attention. In rebellious children especially this is however, more easily directed than accomplished; and it is by no means infrequent to have an undue ardour in making applications followed by the creation of new lesions in the mucous membrane of the throat and nose; to avoid which the spray alone should be used , boracic solutions or hydrogen peroxide I : 10. for the nose, being most

serviceable. The greatest kindness and tact must be used in overcoming the struggles of a refractory child, so that its already lowered vitality may have no further drain upon it in effecting what really accom - plishes so little. In older children a gargle of boracic acid or other anteseptic will usually meet the indication admirably. When suffering from laryngeal diphtheria the child should inhale an admosphere saturated with Löffler's solution, consisting of menthol 10 grams, dissolved in sufficient toluol to make 36 c. c., liquor ferri sesquichlor.,4 c. c., absolute alcohol, 60 c. c. The inhalation of an atmosphere laden with the vapour of slaking lime usually gives marked relief; so also, mercurial fumigation and linseed poultices in cases of laryngeal stenosis.

External applications to the throat, whilst devoid of any effect upon the course of the disease, are useful in relieving the pain and swelling in the cervical lymphatic glands. Massaging of the throat with hot camphorated oil is very grateful, as are the respective liments of soap and chloroform. Poultices, being apt to favour suppuration, should not be used. The local tension may be relieved and inflamation reduced, in older children by the external application of cold, in the form of an ice collar.

DIPHTHERIA ANTITOXIN.

In the year 1890, Behring (Deut. med. Woch., 1890, Nos. 49 and 50; Zeit. f. Hyg., XII, 1, 1892) made the important discovery that the blood of animals rendered immune against diphtheria by inoculation first with attenuated and then with virulent organisms, contained a neutralizing substance - "Anti - Körper - capable of annulling the effects of the bacilli or the toxin when simultaneously or subsequently inoculated into susceptible animals; and this substance - held in the blood - serum of the immunized animals - is the diphtheria antitoxin. The latter is now made by immunizing horses against increasing quantities of diphtheria toxin until the proper degree of immunity has been attained, then withdrawing the antitoxic blood.

PREPARATION OF THE TOXIN.

For from 5 to 7 days, at a temperature of 37°c., the most virulent diphtheria bacilli, obtainable are cultivated in alkaline bouillon, when it will be found that any acidity primarily produced by the bacillus has been replaced by a greater alkalinity than hitherto existing; and the toxin - production appears to keep pace with this alkalinity. To the cultures when "ripe", 0.4 per cent. of trikresol is added, the whole being now either filtered through porcelain or paper, or simply allowed to sediment, as the dead bacilli are not irritating and their presence harmless. Under favourable conditions and with a virulent bacillus,

the filtered culture should be so toxic that 0.001-0.002 would be fatal to a 250- gram guinea - pig within four days.

Park and Williams (Jour., of Experimental Medicine vol 1, No. 1, Jan, 1896, p. 164) state that they found that toxin of a sufficient strength to kill a 400 - gram guinea - pig in three days and a half in a dose of 0.- 0.025 c. c., developed in suitable bouillon, contained in ordinary Eelenmeyer flasks, within a period of 24 hours, In such bouillon the toxin reached its greatest strength in four to seven days - 0.005 c.c. killing a 500 - gram guinea - pig in three days, This period of t time covered that of the greatest growth of the bacilli as shown both by the appearance of the culture and by the number of colonies developing on agar plates. The bodies of the diphtheria bacilli did not at any time contain toxin in considerable amounts. The type of the growth of the bacilli and the rapidity and extent of the production of toxin depended more on the reaction of the bouillon than upon any other single factor. The best results were obtained in bouillon which, after being neutralized to lithmus, had about 7 c.c, of normal soda solution added to each litre. An excessive amount of either acid or alkali prevented the development of toxin. Strong toxin was produced in bouillon containing peptone ranging from 1 to 10 per cent. The strength of the toxin averaged greater in the 2 and 4 per cent, peptone solution than in the 1 per cent.

When the stage of acid reaction was brief and the degree of acidity probably slight, strong toxin developed while the culture bouillon was still acid; but when the stage of acid reaction was prolonged, little, if any toxin was produced until just before the fluid became alkaline, glucose is deleterious to the growth of the diphtheria bacillus and to the production of toxin when it is present in sufficient amounts to cause by its disintegration too great a degree of acidity in the culture fluid. When the acid resulting from the decomposition of glucose is neutralized by the addition of an alkali, the diphtheria bacillus again grows abundantly.-

Smith (jour. of exper. Med., May and July, 1899, p. 373), however, maintains that when the glucose is present in the culture medium in quantities not exceeding 0.2 per cent in peptone bouillon freed from fermentable acid - producing substances, as muscle sugar, it leads to the maximum accumulation of toxin by utilizing the available peptones to the best advantage. With this opinion the writer concurs and believes the strongest toxin can be obtained by fermenting the meat - infusion by adding colon bacilli, and, after the destruction of the muscle sugar, adding 0.1 per cent. of glucose. A less efficacious method than that of Smith is the one suggested by Martin (Ann . de l'Inst. Pasteur Jan. 25, 1898, vol. XII, No. 1,) consisting in the use of a standard peptone in cultures intended to be highly toxic, for which purpose a "bouillon de panse" is pre-

pared by adding 200 grams of finely chopped hogs' stomachs, 10 c.c. of pure hydrochloric acid and 1000 c.c., of water, The mixture is kept at 50. c. for from 12 to 24 hours, during which time the proteids of the stomach are converted into peptones The mixture is then heated to 100.c., to destroy the excess of pepsin, and passed through a cloth. The liquid is warmed again to 80 c. and alkalinised then filtered through paper. After this the temperature is to be elevated to 120 c., and the fluid filtered again through paper, dispensed in flasks, and finally sterilized in the antoclave. The diphtheria bacillus grows abundantly in the medium, without the production of any acid, and produces toxin of which 0.01 c. c. killed a 500 - gram guinea - pig. The mixture can be used as thus prepared or can be mixed with an equal volume of veal infusion. The most appropriate alkalinity of the bouillon seems to be +1.1, determined by titration with phenolphthalein. The toxic bouillon is probably a very complex and by no means stable product. The toxin itself which is the most important constituent, begins to change while the growing culture is still in the incubator, and continues to change subsequently into "toxoids", which are much less poisonous and of different combining affinity. By heating or otherwise manipulating the bouillon a somewhat different change with the formation of "toxons" may be brought about. Toxons are not important, though animals may be immunized against them, but toxoids are important, as will be seen later. According to Wood

(Centralbl. f. Bakt., Mar. 3, 1902, XXXI, No. 6, p. 241) much advantage will result from immunizing animals against what he terms "homoeoplastic toxins", the latter being prepared by allowing the bacteria, which are to furnish the toxin, to grow in media containing the serum of the same species of animal as is subsequently to be immunized. The culture medium was prepared by allowing the blood of the appropriate animals to run into ordinary peptone broth. The mixture, contained in a litre measure, was stood on ice in order that the corpuscles might sediment, after which the supernatant fluid was decanted and filtered through a Chamberland bougie. The serum broth was then inoculated with a virulent diphtheria culture, incubated at 37°c. for a month, them heated at 65°c. for two hours, and finally filtered through a Chamberland candle and subsequently preserved with toluol With this "homoeoplastic toxin" the immunization of animals large and small progressed rapidly, and the antitoxin production took place much more rapidly than with "heteroplastic ~~it~~ toxins."

IMMUNIZATION OF THE ANIMAL%

The horses chosen for inoculation should be young, vigorous, of fair size , and absolutely healthy; and received in the beginning a small dose of the toxin - about 0.1 c. c. - hypodermically so as to detect individual susceptibility. If well borne, in six days a larger dose of toxin may be injected, in six days more a still larger one, the increase being continued every

six days until enormous quantities - 500 or even 1000 c.c. - can be injected at a time. The toxin used usually causes some local reaction, at first a distinct inflammation later a painful oedema and febrile reaction. The amount of local irritation is much less marked when the injections are made slowly and the toxin be allowed to enter the tissues by the gravitation method. Following each injection of toxin, during the period of immunization, is a formation of antitoxin corresponding to the volume and strength of the toxin injected, so that as the doses of toxin increase, the antitoxicity of the blood also increases. It should be noted, however, that the toxin injection is not followed by an immediate rise in the antitoxic value of the blood, but by a peculiar variation in which for about two days succeeding the injection the antitoxic value of the blood diminishes, then by a period in which it gradually rises until by the ninth day subsequently it attains its acme. It is therefore, necessary in order to secure the best results to time the injections so as not to interfere with the highest attainable value of the previous injection, but allow them to follow one another about ten days apart, and to secure the best value of the blood to be withdrawn from the horse by taking it at the time of maximum strength. According to Behring (loc. cit.) mixing the toxin with trichloride of iodine will lessen the irritant effect upon susceptible animals. As the antitoxin perfectly protects the

horse against the toxin, a preliminary dose will enable one to omit all the small preliminary doses of toxin, and render the horse immune forthwith.

PREPARATION OF SERUM FOR THERAPEUTIC PURPOSES.

The horse must be bled when a high degree of immunity has been attained and a test of a small quantity of the blood withdrawn by a hypodermic syringe shows that it is of high antitoxic value. A small incision is made and the blood withdrawn from the jugular vein by means of a sharp-pointed cannula, which is plunged through the vein wall. The blood is received in large flasks and allowed to clot, the flasks being placed at first, while clotting is taking place, in a slanting position. The serum is syphoned off by means of aseptic glass and rubber tubing, and is stored in large flasks. From this, as needed, the serum - which is the antitoxin - is pipetted off into small phials, every precaution being taken to render these absolutely sterile, and to avoid contamination of the serum. The serums can be preserved with camphor, with 0.5 per cent of carbolic acid, by 0.4 per cent of trikresol., or with 1 : 1000 formal dehyde. The dried serum of commerce is not to be recommended as it is somewhat insoluble and much less sterile than the liquid preparation.

STRENGTH OF THE SERUM.-

The strength of the serum, obtained in the manner just described is expressed in what are termed

"immunizing units," "normal serum" being of such a strength that 0.1 c.c. will protect against ten times the least certainly fatal dose of toxin when simultaneously injected into guinea - pigs: each cubic centimetre of this normal serum may be regarded as an " immunizing unit." These terms were introduced by Behring and Ehrlich: since then it has been shown that the strength of the serum could easily be increased tenfold, so that 0.01 c. c. of the serum would protect the guinea - pig against the ten times fatal dose. Each cubic centimetre of this stronger serum was described as an antitoxic unit, and necessarily contained ten immunizing units. Still later it was shown that the limits of strength were by no means reached, so that serums of hundreds of times the normal strength were eventually manufactured. With this increase of strength of the prepared serums the exact meaning of "immunizing unit" gradually came to be obscured, so that now the term is regarded as an expression of strength rather than of quantity.

TESTING ACCORDING TO THE BEHRING EHRLICH METHOD:

The number of units present in a sample of serum can be determined according to the following rules:-

I. Determine accurately the least certainly fatal dose of a sterile diphtheria toxin for a standard guinea pig.

2. Determine accurately the least quantity of the serum that will protect the guinea - pig against ten

times the least certainly fatal dose of toxin.

3. Express the required dose of antitoxic serum as a fraction of a cubic centimetre and multiply it by ten. The result is one unit. Example: It was found that 0.01 c.c. of toxin kills at least 9 out of ten guinea - pigs. It is then regarded as the least certainly fatal dose. Guinea - pigs receive ten times this dose (0.1 c.c.) and varying quantities of the serum, measuring by dilution - say $\frac{1}{1000}$ c.c., $\frac{1}{2500}$ c.c., $\frac{1}{5000}$ c.c. The first two live. The fraction $\frac{1}{2500}$ is now multiplied by 10; $\frac{1}{2500}$ X. 10 = 1 unit, with the result that each cubic centimetre of the serum contains 250 units. An immunizing unit may, therefore be defined as ten times the least amount of antitoxin serum that will protect a standard (500 - gram) guinea - pig against ten times the least certainly fatal dose of diphtheria toxin.

EHRLICH'S METHOD OF TESTING.-

Ehrlich (klinisches Jahrb., 1897), in view of the accuracy of the test just described depending upon the ability of one unit of antitoxin exactly to neutralize one unit of toxin states that although the majority of properly made toxins have about the same combining power, they do not necessarily correspond in this particular, as when the cultures are allowed to remain too long in the incubating oven, or are kept on hand for some time subsequently, the toxin formed by the bacilli is transformed into certain other bodies, which

he calls "Toxoids". This makes the greatest fifference as the toxoids have entirely different combining powers from the toxin and may, therefore cause confusion. Thus, a diphtheria bouillon rich in "toxin" when used for testing antitoxin, will make its unit strength appear much greater than an old bouillon rich in "toxoids", because of the smaller minimum fatal dose of the former and larger combining dose of the latter. The toxoids consist of three groups, described as "protoxoids," because they have a greater affinity for the antitoxin union than the toxins; "Syntoxoids," which have an equal affinity for the antitoxin; and "epitoxoids" which have less affinity for the antitoxin than the toxin Ehrlich determined the existence of these bodies by finding the exact limits of toxin- antitoxin. neutralization and toxin - antitoxin fatality. The point at which a mixture of toxin and antitoxin is inactive he describes as L_o; that at which such a mixture becomes fatal by the addition of a little more toxin as L_+. The differences between L_o And L_+ should exactly equal one minimum fatal dose of toxin, but only does so when no excess of epitoxoid is present. When epitoxoids are present and have to be displaced by the added toxins the difference between L_o and L_+ may become enormous. Thus, in one fresh, active toxin Ehrlich found L_o = 50 doses of toxin, L_+ = 100 doses of toxin, the difference between L_o and L_+ not being one single minimum fatal dose, but fifty of them. It follows, therefore that all calculations based upon L_o or upon the exact neutraliza-

tion of the toxin by the antitoxin, as in the original method of testing, must be erroneous, because the combining powers of the antitoxin may not be exhausted in such a mixture. L_+ should, therefore, always be determined and made use of as the test dose.

Ehrlich has suggested the following alterations in the directions for testing the diphtheria antitoxin, for the reason that the dertermination of L_+ must depend upon a standard unit of antitoxin by which it can be determined:-

1. As a standard for the estimation of the antitoxin an antitoxin powder of accurately determined strength, protected against the influence of oxygen and water, is employed. This is contained in carefully measured quantities in specially prepared vacuum tubes. The apparatus at the time present in the laboratory are filled each with 2 grams of a dry antitoxin 700 times the normal strength.

2. To secure the greatest possible degree of permanence the antitoxin should be dissolved in a mixture of equal parts of 10 per cent. solution of Sodium chloride and glycerin. A tube is to be opened every three months and a new solution prepared. Of the dry antitoxin at the time preserved in the laboratory, the contents of a tube are dissolved in 200 c.c. of the mixture described, and thus a test antitoxin solution 17 times the normal strength is prepared.

3. The present test - dose of toxin is determined, with the aid of an immunity unit, such as is contained,

for instance in 1 c.c. of a $\frac{1}{17}$ dilution of the test antitoxin 17 times the normal strength. To this amount of antitoxin increasing amounts of toxin are added, and by means of most careful experimental observations the limit is determined at which just that excess of toxin becomes manifest which causes death of the animal in the first four days. The amount of toxin thus obtained represents the immediate test - dose. By means of the same dose of serum, for the more exact characterization of the toxin, the determination of a second limit is made, for the purpose of learning the dose of toxin that is just neutralized by admixture with the amount of serum named.

4. The determination of the strength of a diphtheria antitoxin is made by means of the test - dose of toxin, as follows:- The test - dose of toxin in question (for instance 0. 355 c.c. of tested toxin at the time present in the laboratory) is mixed with 4 c.c. of antitoxin corresponding to the test figures given. As the test - dose of toxin is estimated for 1. c.c. of antitoxin of normal strength or for 4 c.c. of antitoxin one - fourth of the normal strength, an antitoxin of X strength will have to be diluted $\frac{1}{4}X$, and in testing an antitoxin 100 times the normal strength, $\frac{1}{400}$.

It is of supreme importance that the antitoxic serum for therapentic purposes be as strong as possible as the quantity to be injected at each dose diminishes according to the number of units per cubic centimetre

Year	Number of Cases admitted	Deaths	Mortality per cent. of patients treated	Annual mortality per 1,000 of estimated population.
1888	99	46	59.35	0.32
1889	722	275	40.74	0.39
1890	942	316	33.55	0.33
1891	1,312	397	30.63	0.32
1892	2,009	583	29.35	0.46
1893	2,848	865	30.42	0.76
1894 *	3,666	1,035	29.29	0.62
1895	3,635	820	22.85	0.54
1896	4,508	948	21.20	0.60
1897	5,673	987	17.69	0.51
1898	6,566	991	15.37	0.39
1899	8,676	1,182	13.95	0.43
1900	7,873	988	12.27	0.34
1901	7,622	849	11.15	0.29

the serum contains. None of the methods of concentration - E. g., the partial evaporation of the serum in vacuo - so far suggested can be considered as really satisfactory. According to Bujivid (Centralbl. f. Bakt., etc., Sept., 1897, Bd. XXII, Nos 10 and 11, p. 287) and Ernst (Jour. Boston Soc. of Med. Sci., May, 1898, Vol. II, No. 8, p. 137) when an antitoxic serum is frozen and then thawed, it separates into two layers, the upper stratum watery, the lower yellowish, the antitoxic value of the yellowish layer being about three times that of the original serum, the upper layer consisting chiefly of water.

THERAPEUTIC USE OF ANTITOXIN.

VALUE OF ANTITOXIN.

Mortality from Diphtheria.

All but those harbouring a most Extreme bias towards antitoxin are in accord as to the immense value of the remedy in the treatment of diphtheria to which the following statistics will bear witness.

CASES OF DIPHTHERIA IN THE HOSPITALS OF THE METROPOLITAN ASYLUMS BOARD.

✳ N. B.- In this year antitoxic treatment was commenced since when, as shown by the table there has been a progressive fall in the case mortality.

CASES OF DIPHTHERIA AND CROUP BY QUARTERS DURING YEARS 1891-1900,
OLD CITY OF NEW YORK.

Quarters	1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	Total.
First	1499	1712	1647	2699	2,788	3,235	3,171	2259	2048	2680	23,738
Second	1213	1450	1628	2920	3,052	3,422	3,488	2087	2245	2401	23,904
Third	947	1396	1346	1827	2,048	2,045	2,081	1234	1531	1340	15,322
Fourth	1678	1126	2400	2195	2,465	2,697	2,156	1593	2418	1943	20,671
Total..	5346	5184	7021	9641	10,353	11,399	10,896	7173	8240	8364	83,635

DEATHS FROM DIPHTHERIA AND CROUP BY QUARTERS. CITY OF NEW YORK FROM 1891 to 1897; BOROUGHS OF MANHATTON AND BRONX, 1898 to 1900.

	Quarters	Females 0	1	2	3	4	Total under 5	Females 5-10	10-15	15-20	20-25	25-35	35-45	45-55	55-65	65-75	75-85	Total
1891	First	29	58	56	46	28	217	46	3	1	2	1	"	1	"	"	"	271
	Second	18	47	43	28	18	154	33	"	1	2	"	"	"	1	"	"	191
	Third	17	37	46	37	14	151	29	2	1	1	"	"	"	"	"	"	186
	Fourth	21	60	58	56	35	230	64	5	1	1	1	"	2	"	"	"	305
	Year	85	202	203	167	95	752	172	10	3	8	3	1	1	2	1	"	953
1892	First.	18	59	68	60	24	229	45	2	"	3	2	1	1	1	"	"	284
	Second	22	71	50	48	28	219	45	4	1	2	1	"	"	"	"	"	272
	Third	9	25	35	29	27	125	29	3	"	1	"	"	1	1	"	"	160
	FourtR	18	67	52	44	29	210	54	3	2	1	1	"	"	"	"	"	271
	Year	67	222	205	181	108	783	173	12	3	7	4	1	2	2	"	"	987
1893	First	31	79	65	57	35	267	57	5	3	"	1	4	3	"	1	"	341
	Second	28	59	72	50	29	238	61	4	4	1	"	"	"	"	"	"	308
	Third	24	60	47	28	27	186	41	4	1	"	2	"	1	"	"	"	235
	Fourth	27	75	92	64	46	304	102	9	2	1	1	"	1	"	"	1	421
	Year	110	273	276	199	137	995	261	22	10	2	4	4	5	"	1	"	1305
1894	First	44	102	97	63	44	350	64	5	"	2	1	1	1	"	"	"	424
	Second	30	99	101	80	60	370	76	3	2	2	4	1	"	"	"	"	458
	Third	14	51	42	42	22	171	65	3	"	"	1	"	1	"	"	"	246
	Fourth	21	49	66	43	41	220	50	4	"	"	1	1	1	"	1	"	278
	Year	109	301	306	228	167	1111	255	20	2	4	7	3	3	"	1	"	1406
1895	First	33	67	71	31	29	231	44	4	1	"	1	"	1	"	"	"	282
	Second	30	57	48	36	35	206	50	2	2	"	1	"	"	1	"	"	262
	Third	6	57	53	36	15	167	32	5	"	1	"	"	"	"	"	"	205
	Fourth	15	51	45	35	15	161	43	1	1	"	3	1	"	"	"	"	210
	Year	84	232	217	138	94	765	169	12	4	1	5	1	1	1	"	"	959
1896	First	23	67	71	44	28	233	36	5	2	1	3	1	1	"	"	"	282
	Second	19	53	50	39	34	195	46	6	"	1	2	"	"	"	"	"	250
	Third	16	40	35	28	26	145	28	4	1	"	"	"	"	"	"	"	178
	Fourth	7	37	32	30	13	119	41	1	"	3	1	"	"	"	"	"	165
	Year	65	197	188	141	101	692	151	16	3	5	6	1	1	"	"	"	875
1897	First	27	59	53	43	23	205	30	2	"	"	1	2	"	1	"	"	244
	Second	24	71	49	42	18	204	67	2	"	1	1	"	"	"	"	"	275
	Third	9	41	26	21	18	115	28	1	1	1	"	"	"	"	"	"	146
	Fourth	14	42	25	16	17	114	39	1	"	"	1	"	"	"	"	"	155
	Year	74	213	156	122	76	641	146	6	1	2	3	2	"	1	"	"	820

		MALES								MALES								
	Quarter	0	1	2	3	4	Total under 5	5	10	15	20	25	35	45	55	65	75	85	Total
1898	First	14	34	32	19	13	112	34	6	"	"	1	1	"	"	"	"	"	154
	Second	8	25	17	21	13	84	17	2	"	"	"	"	"	"	"	"	"	104
	Third	4	14	21	12	5	56	15	1	"	"	"	"	"	"	"	"	"	72
	Fourth	9	22	24	9	17	81	26	2	1	"	1	1	"	"	"	"	"	118
	Year	35	101	94	61	48	339	92	11	1	"	3	2	"	"	"	"	"	443
1899	First	11	46	30	22	14	123	18	1	"	"	3	"	"	1	"	"	"	146
	Second	18	38	24	23	15	119	21	3	1	1	"	1	"	"	"	"	"	146
	Third	12	27	22	14	10	85	14	1	2	"	2	"	1	1	"	"	"	110
	Fourth	11	37	32	27	20	127	25	3	"	"	2	"	"	1	"	"	"	153
	Year	52	149	112	86	59	458	78	8	3	1	7	1	1	3	"	"	"	560
1900	First	31	51	37	23	28	164	41	1	1	3	4	2	1	"	"	"	"	216
	Second	7	36	41	38	24	146	38	"	"	"	1	1	"	"	"	"	"	186
	Third	10	8	12	11	14	55	18	5	"	"	1	"	1	"	1	"	"	80
	Fourth	16	13	23	17	15	86	29	6	"	3	1	"	"	"	"	"	"	125
	Year	64	108	115	89	75	451	126	12	1	6	7	3	"	"	1	"	"	507
1891	First	40	61	59	43	22	224	32	3	"	1	"	3	"	1	"	"	"	264
	Second	28	62	50	32	29	201	30	2	2	"	2	2	"	"	"	"	"	239
	Third	18	41	35	41	24	159	36	1	"	1	"	"	1	"	"	"	"	198
	Fourth	25	68	67	57	36	253	57	2	"	2	2	"	"	"	"	"	"	316
	Year	111	232	210	173	111	837	155	8	2	4	4	5	1	1	"	"	"	1017
1892	First	27	178	85	56	27	273	34	1	2	"	2	1	1	"	"	"	"	314
	Second	24	59	71	43	29	226	47	3	1	1	"	1	1	"	1	"	"	281
	Third	20	58	50	42	26	196	29	3	"	"	"	"	1	"	"	"	"	229
	Fourth	21	74	64	46	41	246	38	5	1	2	"	2	1	"	"	"	"	295
	Year	92	269	270	187	123	941	148	12	4	3	2	4	4	"	1	"	"	1119
1893	First	35	32	80	65	26	238	44	2	"	"	"	1	1	"	1	"	"	337
	Second	30	75	67	48	26	246	44	2	"	"	"	1	1	1	"	"	"	295
	Third	11	68	52	41	32	204	37	4	1	1	"	"	"	"	"	"	"	247
	Fourth	22	75	79	64	37	277	86	7	1	2	"	"	"	"	1	"	"	374
	Year	98	300	278	218	121	1015	211	15	2	3	"	2	2	1	2	"	"	1353
1894	First	42	120	102	77	54	395	61	6	"	"	2	"	"	"	"	"	"	464
	Second	37	92	94	79	49	351	70	2	1	1	"	"	"	"	"	"	"	425
	Third	21	61	58	49	28	217	48	1	"	"	1	"	"	"	"	"	"	267
	Fourth	25	78	57	48	36	244	54	7	1	1	"	"	1	"	"	"	"	308
	Year	125	351	311	253	167	1207	233	16	2	2	3	"	1	"	"	"	"	1464
1895	First	49	80	56	50	30	265	33	"	1	1	1	1	"	"	"	"	"	302
	Second	45	68	57	50	24	244	49	3	1	"	2	"	"	1	"	"	"	300
	Third	17	48	42	29	24	160	24	2	2	"	2	1	1	"	"	"	"	192
	Fourth	19	51	45	46	24	185	32	3	"	"	1	1	"	1	"	"	"	223
	Year	130	247	200	175	102	854	138	8	4	1	6	3	1	2	"	"	"	1017
1896	First	31	86	51	28	30	226	33	4	"	1	3	2	2	"	"	"	"	271
	Second	33	67	62	25	26	213	33	2	"	2	2	"	"	"	"	"	"	253
	Third	11	40	40	18	23	132	21	4	"	"	"	"	"	"	"	"	"	157
	Fourth	21	48	40	41	21	171	32	1	"	"	2	"	1	"	"	"	"	207
	Year	96	241	193	112	100	742	119	11	1	1	7	4	3	"	"	"	"	888
1897	First	33	45	57	31	22	188	25	2	"	2	"	1	"	"	"	"	"	218
	Second	26	68	49	26	23	192	44	4	"	1	2	"	"	"	"	"	"	243
	Third	11	46	36	27	12	132	26	1	3	"	1	"	1	"	"	"	"	164
	Fourth	12	37	27	22	18	116	23	3	1	1	"	1	"	"	"	"	"	145
	Year	82	196	169	106	75	628	118	10	4	4	3	2	1	"	"	"	"	770
1898	First	21	50	26	17	11	125	19	3	1	2	3	"	2	"	2	"	1	156
	Second	12	44	26	16	15	113	15	1	"	"	1	"	"	"	"	"	"	130
	Third	7	19	16	12	7	61	13	2	"	"	"	"	"	1	"	"	"	77
	Fourth	12	36	23	12	9	92	12	"	"	1	2	"	1	"	"	"	"	108
	Year	52	149	91	57	42	391	59	6	1	3	6	"	3	1	1	"	"	471
1899	First	22	42	25	23	9	121	11	1	"	"	1	"	"	"	"	"	"	134
	Second	19	29	29	17	15	109	24	4	1	"	4	"	"	"	"	"	"	142
	Third	6	31	19	19	9	84	14	1	"	"	"	"	"	"	"	"	"	99
	Fourth	15	31	34	29	12	121	27	1	"	"	1	"	"	"	"	"	"	150
	Year	62	133	107	88	45	435	76	7	1	"	6	"	"	"	"	"	"	525
1900	First	24	55	38	38	19	174	29	2	1	1	1	"	"	1	"	"	"	209
	Second	27	42	38	34	15	156	45	3	1	"	3	2	"	"	"	"	"	209
	Third	4	23	13	20	13	73	18	4	4	"	3	"	"	"	"	"	"	102
	Fourth	17	27	27	27	15	113	22	8	3	"	2	"	"	1	"	"	"	99
	Year	72	147	116	119	62	516	114	17	8	1	9	2	"	2	"	"	"	669

The above tables show the large number of cases of diphtheria occurring in New York City during the periods named, where now, as elsewhere the death - rate from the disease has decreased under antitoxin, roughly about 50 per cent., and it seems daily to be decreasing with improvements in the manufacture of the serum and its general adoption, especially early in the disease. In New York City the antitoxin, though introduced in 1895 did not come into general use until a few years later. The following tables display results there before and after its adoption:-

Without Antitoxin.

Year	Cases Reported	Deaths	Mortality Percentage
1891	5,364	1,970	36.7
1892	5,184	2,106	40.0
1893	7,021	2,558	36.4
1894	9,641	2,870	29.7
Total	27,210	9,504	Average 34.9

With Antitoxin

Year	Cases Reported	Deaths	Percentage Mortality
1895	10,353	1,976	19.0
1896	11,399	1,763	15.5
1897	10,896	1,590	14.5
1898	7 ,173	919	12.8
1899	8,240	1,085	13.1
1900	8,364	1,176	14.0
Total	56,425	8,509	Average.15 per cent.

Average for last four years 13.6 per cent

From the above it follows that with the introduction of antitoxin the death - rate in New York City has

been reduced by 58 per cent., that is, has fallen from 34.9 per cent. to 15 per cent. Taking, however, from 1897 to 1900, during which time the antitoxin came to be more generally used, one finds a death - rate of 13.6 per cent., or a reduction in mortality of 64 per cent.

The Report of the American Pediatric Society collective Investigation for 1896 clearly demonstrates the great value of antitoxin in private practice. The following is a summary of the Society's results:-

(1) The report includes returns from 615 physicians Of this number more than 600 have pronounced themselves as strongly in favour of the serum - treatment, the great majority being enthusiastic in their advocacy.

(2) The cases included have been drawn from localities widely separated from each other, so that any peculiarity of local conditions to which the favourable reports might be ascribed must be excluded.

(3) The report includes the record of every case returned except those in which the evidence of diphtheria was clearly questionable. It will be noted that doubtful cases that recovered have been excluded, while doubtful cases that were fatal have been included.

(4) No new cases of sudden death immediately after injection have been returned.

(5) The number of cases injected reasonably early, and in which the serum appeared not to influence the progress of the disease, was about 19, these being made

up of 9 cases of somewhat doubtful diagnosis, 4 cases of diphtheria complicating measles, and 3 malignant cases in which the progress was so rapid that they had passed beyond any reasonable prospect of recovery before the serum was used. In two of these the serum was of uncertain strength and of doubtful value.

(6) The number of cases in which patients appeared to have been made worse by serum was 3, and among these there is only 1 case in which the result may be fairly attributed to the injection.

(7) The general mortality in the 5794 cases reported was 12.3 per cent., and excluding all cases moribund at the time of injection or dying within 24 hours it was 8.8 per cent.

(8) The most striking improvement was seen in cases that were injected during the first 3 days. Of 4120 such cases the mortality was 7.3 per cent., and, excluding cases moribund at the time of injection or dying within 24 hours, it was 4.8 per cent.

(9) The mortality in 1448 cases injected on or after the fourth day was 27 per cent.

(10) The most convincing argument, and to the minds of the committee, an absolutely unanswerable one, in favour of serumtherapy is found in the results obtained in the 1256 laryngeal cases (membranous croup). In one-half of these, in a large proportion of which the symptoms were severe, recovery took place without operation. Among the 533 in which intubation was performed the mortality was 25.9 per cent., or less than half as great as has ever been reported by any, form of

treat

treatment.

(11) The proportion of cases of broncho - pneumonia (5.9) per cent.) is very small and in striking contrast to results published from hospital sources.

(12) As against the two or three instances in which the serum is believed to have acted unfavourably upon the heart may be cited a large number in which there was a distinct improvement in the heart's action after the serum was injected.

(13) There is very little if any evidence to show that nephritis was caused in any case by the injection of serum. The number of cases of genuine nephritis is remarkably small, the deaths from that source numbering but 15.

(14) The effect of the serum on the nervous system is less marked than upon any other part of the body; paralytic sequelae being recorded in 9.7 per cent of the cases, the reports going to show that the protection offered by the serum is not great unless injections are made early.

Other statistics from various parts of the globe show the same reduction in death - rate consequent upon the use of the antitoxin. a few examples may be given in order to make proof as conclusive as possible:-

Amongst the most striking statistics on record are those published by the Health Department of Chicago, from which it appears that five years prior to the introduction of antitoxin there that been 7,411 deaths

from diphtheria and croup, that is an average of 1,482 deaths = a death rate per annum of 11.23 per 10,000 of the population. From 1895 (antitoxin being introduced on the 5th. of October of that year) during the five years ending December 31st., 1900 the aggregate number of deaths from diphtheria and croup was 4,309, = an annual average of 862 deaths and an annual death - rate of 5.45 per 10,000 of population. From these figures it is apparent that there was a reduction upon the first - year pre - antitoxin period of nearly 42 (41.96) per cent in the actual numbers and of nearly 52 (51.72) per cent. in the death - rate. The case mortality of diagnosed diphtheria during the years 1891 to 1895 averaged about 35 per cent. During the 63 consecutive months between October 1895 and December 1900 the case - mortality was less than 7 (6.79) per cent. = a reduction of 80 per cent. upon the pre - antitoxin rate. In Chicago it is the custom of the Inspectors of the Health Department to visit every case of sore throat: if it be suspicious, antitoxin is used without waiting for a bacteriologic examination; hence a large proportion of the cases are treated within the first day or two of the disease; and every case of "sore throat" is examined bacteriologically. The record of 5,727 cases shows 2 deaths in 476 treated on the first day of the disease = a mortality rate of 0.42 per cent; 22 deaths in 1,426 cases first treated on the second day = a mortality rate of 1.54 per cent.; 73 deaths in 2,034 cases first treated on the third day = a

mortality rate of 3.59 per cent.; while there were 118 deaths in the 1,037 cases first treated on the fourth day of the disease = a mortality rate of 11.38 per cent; and 174 deaths in the 754 cases treated later than the fourth day, or over 23 per cent. The urgent importance of early treatment is strikingly apparent, especially when one considers how in the 3,936 case of diphtheria treated with full doses of antitoxin on the third day of the disease or earlier there were 97 deaths = a mortality rate of less than two and one - half per cent. (2.46 per cent); whereas in the remaining 1,491 cases first treated on the fourth day or later there were 292 deaths = a mortality rate of more than 19.5 per cent

The statistics from the Imperial Board of Health of Berlin, 1895 - 1896 (furnished by 285 physicians from 204 public institutions) show 13,137 cases - extended over 18 months - with a mortality of 15.8 per cent, The mortality of cases treated on the first day was 6.6 per cent.; second day 8.3 per cent.; third day 12,9 per cent.; fourth day 17 per cent,; fifth day, 23.3 per cent.

The following instructive table is from Biggs and Guerard:-

Treated on:-	Cases.	Deaths.	Mortality percentage
First day of the disease	1415	51	3.5
Second " " " "	2640	213	8.0
Third " " " "	2340	300	12.8
Fourth " " " "	1458	346	23.6
Fifth day and after "	1912	671	35.0
Total.	9765	1581	16.1

Moreover, if additional proof of the desirability of serumtherapy in diphtheria were needed it may be noted that estimated on the money basis of the value of human life, the saving of life during the antitoxin period in 1900 represented a saving of nearly a million and a half pounds. Burrows (Amer. Jour. Med. Sci.) Feb. 1901, p. 125) states that there were (in February 1901) 2093 cases of diphtheria in the Boston City Hospital, of which 1962 were ~~the~~ uncomplicated: among the latter there was a mortality of 12,23 per cent., or, deducting 69 moribund cases, 9 per cent. In Boston City itself, the death - rate was 30.75 per cent. from 1880 to 1894 but only 12.6 per cent. from 1895 to 1897.

Welch ("The Treatment of Diphtheria" by Antitoxin"- Trans. Assoc. Amer. Physicians, p. 313, 1895) has analysed 82 reports in Europe and America containing 7166 cases showing a mortality of 17.3 per cent. as compared with a minimum of mortality of 42.1 per cent. = a reduction of 55 per cent.

Mortality according to Age:-

Even when antitoxin be used, the younger the patient the higher the death rate, as will be seen from the following tables:-

Table 1. - Biggs and Guerard (Jour. Amer. Med. Assoc., Mar. 17, 1900, p. 695).

TREATED WITHOUT ANTITOXIN.

Ages	Cases.	Deaths.	Mortality.
0--2 years	1494	469	31.4 per cent
2--5 "	3678	762	20.7 " "
5--10 "	3164	473	14.8 " "
Over 10 years	1444	99	6.9 " "

Table II.- Baginsky ("Diphtherie u. diphtheritischer Kroup"- Nothnagel's Pathol. "Wien, 1898)

TREATED WITHOUT ANTITOXIN.

Ages.	Mortality.
0--2 years	63.3 per cent.
2--4 "	52.8 " "
4--6 "	37.9 " "
6--10 "	24.6 " "
10--15 "	14.6 " "

(N B. - Comparison of Tables I and II shows that diphtheria is still a very fatal disease of infancy).

Table III.- Burroughs (loc.cit)-Boston City Hospital 1900.

TREATED WITH ANTITOXIN.

Age	Mortality.
0--1 Years	40.00 per cent.
1--2 Years	33.00 " "
2--3 "	23.00 " "
4--5 "	15.60 " "
5--6 "	14.60 " "
6--7 "	12.30 " "
7--8 "	14.00 " "
8--9 "	8.60 " "
9--10 "	2.08 " "

Note.- Amongst patients under 5 years of age the death rate was 21.30 per cent., 5 to 10 years 8.40 per cent.; 10 to 15 years, 3.10 per cent.

Antitoxin in Laryngeal Cases.-

The immense value of antitoxin is perhaps most strikingly seen in laryngeal cases, the mortality being reduced (1) by its effect upon operated cases -intubation and tracheotomy ; and (2) by decreasing the number of cases which come to operation.

Thus, Mc. Naughton and Maddren ("Intubation," Med. News, New York, May 15, 1897) show a death rate of 69.5 per cent among 5546 intubated cases (1892), and state that the present mortality amongst such, treated with antitoxin, is only 27.24 per cent.; that the mortality of laryngeal diphtheria is 21.2 per cent., and that about 60 per cent. have not required operation.

Burrows (loc. cit.) amongst 1,962 cases of diphtheria had 337 cases with laryngeal stenosis, of which same 213 were intubed, but the remaining 124 responded promptly to the use of antitoxin and were relieved without the necessity for intubation. Of the 213 intubations, 96 died; reintubation was necessary in many cases, in one as many as 13 times. Of the intubations a subsequent tracheotomy was required in three.

Mc Cullom ("A Clinical Study of 800 Cases of Diphtheria at Boston City Hospital" Boston Med. and Surg. Reports, 1898, IX; "Antitoxin in Diphtheria" - Boston Med. and Surg. Jour., 1898, CXXXIX, 153 - 156) states that up to 1895 the mortality in his intubated cases was 83 per cent., but from ~~k~~ 1895 to 1898, 55 per cent.

In the Report of the American Pediatric Society on the antitoxin treatment of laryngeal diphtheria in

private practice it is stated that there were 1704 cases, with a death - rate of 21.19 per cent. of these 60.79 (1036 cases) did not require operation, and the mortality was 17.18 per cent.; in 637 intubated cases, 166 deaths = a mortality of 26.05 per cent. Comparing these results with those of Mc.Cullum the greater mortality in hospitals is apparent. In the 20 tracheotomized cases reported in private practice by the Society there were 9 deaths = 45 per cent,; intubation and tracheotomy. 11 cases, with 7 deaths = 63.63 per cent.

Goodall (Brit. Med Jour. 1899,1, pp. 197 and 268) has collected a mass of statistics from which it appears that about 33 per cent. only of all laryngeal cases, whether operated upon or not, recovered before the introduction of antitoxin; while of the cases not operated upon about 47 per cent, and of the tracheotomy cases not more than about 29 per cent recovered. Since the use of antitoxin, of all laryngeal cases about 72 per cent. recover, while of the cases not operated upon about 80 per cent., and of the tracheotomy cases about 63 per cent., recover.

The Metropolitan Asylums Board Report for 1900 gives 477 laryngeal cases treated with antitoxin, with 182 deaths. Amongst the cases were 377 tracheotomies, with 127 deaths, or 33.65 per cent.

In 1894 without antitoxin, there were over 1800 with 73 per cent. of deaths; in 1896, with antitoxin, 137 cases, with a mortality of 43.7 per cent.

In 1898 the Investigation Committee of the Clinical

Society of London report 75 cases of tracheotomy, with antitoxin treatment, and 27 deaths, or 36 per cent., as compared with a previous mortality of 71.6 per cent. without antitoxin. Analysing the 75 cases, we find that - treated from the first to the third day, there were 31 cases, 5 deaths = 16.1 per cent,; fourth to sixth day 27 cases, 11 deaths = 40.7 per cent.; on and after seventh day, 17 cases, 11 deaths = 64.7 per cent.

Returning to the statistics of the Imperial Board of Health of Berlin, it appears there were 4085 laryngeal cases, 2744 of which were operated on with a mortality of 32.3 per cent.

Clubbe (Brit. Med. Jour., Vol. XI, p. 1177, 1897) mentions 300 laryngeal cases with 129 tracheotomies, with a death - rate of 20 per cent.; and 300 cases treated with antitoxin, with 199 tracheotomies and 158 deaths, or 52.7 per cent.

Effect of Antitoxin on Eye Cases.-

The value of Antitoxin in relieving diphtheritic eye affections has now been established. Thus, Mc.Cullum (loc. cit.) reports 15 cases of conjunctival diphtheria at the Boston City Hospital in every one of which the eye would inevitably have been lost but for the antitoxin injection which every case received.

Antitoxin and Diphtheritic Paralysis.-

The effect of the antitoxin upon the occurrence of paralysis is not easy to determine: its incidence appears, however, to have increased slightly, according to Woollacott (Lancet, 1899, II, p. 561), since

the introduction of the remedy; and this is generally believed to be due to the fact that more cases, especially the serious ones, recover now than formerly, and consequently more cases of paralysis are met with.

From a series of experiments upon the occurrence of paralysis after the injection of toxin and antitoxin Ransom (Jour. Pathol. and Bacteriol., VI, No. IV., 1900 p. 397) has arrived at the following conclusions:-

1. Paralysis may certainly be expected to occur after inoculation with not less than one - fourth of the minimum fatal dose. With doses between one - fourth and one - eighth paralyses are not constant. With weaker than one - eighth, no paralysis.

2. If the animal survives long enough the larger the dose of toxin, the more severe the paralysis.

3. Neutralized mixtures of toxin and antitoxin containing only about one lethal dose or less do not appear to cause paralysis.

4. Antitoxin given 15 to 22 hours after intoxication with doses of toxin not greater than the lethal dose exercises in large doses a modifying influence on the subsequent paralysis. This influence is more marked on smaller doses of toxin than on such as are but little less than the minimum fatal dose. Small doses of antitoxin have no evident effect in diminishing the paralysis.

5. In human beings we may thus expect liberal doses of antitoxin, given early, to influence favourably the subsequent paralysis, and this influence is

likely to manifest itself not so much on the local paralysis (palate, etc.) as on such symptoms as heart failure. Severe cases are likely to be followed by severe paralysis, in spite of large doses of antitoxin.

The following statistics published by the London Clinical Society, 1898, will serve to substantiate Ransom's views:-

There were 145 cases of paralysis in 633 cases treated with antitoxin, or 22.9 per cent.- in ~~cases~~ 110 cases slight, in 35 cases severe; but in another series of cases treated without antitoxin, paralysis occurred in only 10,8 per cent. The mortality, however, among the cases treated with antitoxin was 8.9 per cent and 12.2 in those not so treated. The cases treated with antitoxin averaged, by days, thus:-

Time on Treatment.	Cases.	Paralysis	Slight	Severe	Percentage
On the 1st. day	20	1	1	0	5.0
" " 2nd. "	92	15	14	0	16.3
" " 3rd. "	133	34	29	5	25.5
" " 4th. "	130	28	22	6	21.5
" 5th. to 10th day.	- - -	- - -	- - - -	2	25.9

It is usually believed that the antitoxin has no effect, Except in cases treated early, as the toxaemia - the cause of the paralysis, has already begun to effect the nerves; and that in severe cases with much toxaemia paralysis will occur with or without antitoxin if the patient lives long enough, the paralysis being probably prevented if the antitoxin be used early and in sufficient doses.

Effect on the kidneys.-

No matter to what kind of patient antitoxin be given a slight albuminuria is invariably produced. This however, is only transient according to Michael's analysis of the returns ("Complications with Antitoxin Use", Practitioner, 1898, LX, 371-383) of the London Metropolitan Asylums Board, 1893, albuminuria in 24.1 per cent. in 1894, in 40 per cent in 1895, and in 60.1 per cent. in 1896 with the use of antitoxin. In 1894 Nephritis occurred in 1.2 per cent, of the cases; in 1895 in 2 per cent.; in 1896, with antitoxin, in 0.5 per cent.

Mc.Cullum (loc. cit.) reports that amongst the 173 patients at the Boston City Hospital no albuminuria occurred before or after antitoxin in 99; in 23 the albumin remained unchanged after injection; in 16 it was slightly increased; in 25 diminished.

The injection of antitoxin seems to have the effect of diminishing the amount of urine for several days even in non - diphtheritic patients. some, however, deny this finding and reports polyuria.

Effect on the Heart.-

No one has yet been able to prove that antitoxin produces cardiac complications when used early, that is before the third or fourth day.

Effect upon the Occurrence of Broncho - pneumonia.-

This being the complication most to be dreaded in diphtheria, it is pleasing to find that antitoxin which is a specific for the latter disease by cutting

it short has reduced greatly the mortality from the former and generally made the cases of it less serious than hitherto.

Dosage of Antitoxin.-

Writers are at variance as to the dose of antitoxin to be administered. The tendency in the early days of the treatment was to give it in too small doses. usually from 2000 to 3000 units will suffice for a child of over a year suffering from an ordinary attack of diphtheria; but it is advisable to use from 3000 to 5000 units for laryngeal and severe cases of any age. Children under one year should have 1500 to 2000 units. These doses if necessary can be repeated every 12 hours until three have been given. The serum used should be as concentrated as possible. No specially constructed syringe - provided it will hold 5 c.c.- is needed. Due antiseptic precautions, must of course be observed with it and the part of the skin to be penetrated. The latter is usually the abdomen, the thigh or posterior axillary line. The occurrence of abscesses after the operation will indicate carelessness in technique, as nothing beyond a slight redness and oedema should be observed to follow the injection.

It will not be long before the false membrane will be seen to undergo change. In typical diphtheria within a few hours of the operation the Exudate will be seen to become blanched, less dirty looking to swell, to become more or less granular and thicker, with

swelling, congestion and purplish discolouration of the surrounding mucous membrane. Soon the false membrane becomes loosened at the edges and rolled up and detaches itself either in one or several small pieces, or, failing that can be washed off. In from 24 hours to four days the mucous membrane of the part returns to normal. Should the membrane reappear another dose of antitoxin will be needed. Similar effects are observed in parts other than the fauces and tonsils. The temperature steadily falls unless some complication be present. Thus Mc.Cullum, in an analysis of 800 cases, found that 121 fatal cases had a temperature above 103° F.; the remaining 105, a temperature from normal to 103° F (the antopsy in every case revealed complications), of 679 non - fatal cases, only 55 had a temperature of 103° F. or over.

ANTITOXIN EXANTHEMATA

Anyone experienced in the use of antitoxin will have observed the occurrence of rashes after its use with more or less frequency. Thus, in 633 cases examined the Investigation Committee of the Chinical Society report the occurrence of a rash in 34.7 per cent of the 220 cases. Of these, the rash in 161 was erythematous, urticarial in 37, mixed in 17, and petechial in 5, and of the last mentioned number 2 died. In 136 cases the rash was accompanied by a high temperature, and in all but 46 of the cases it was first seen at the site of injection. The exanthem was observed to

appear as follows:- First to sixth day - 33 cases; seventh to twelfth day - 147 cases; thirteenth to eighteenth day - 34 cases; nineteenth to thirty - first day - 6 cases. The average duration of the rash was 1 to 5 days, and it recurred in 11 cases.

Berg ("Serum Examthemata" - New York Med Rec., 1898, LIII, 865 - 873) observed that the rash occurred 82 times in his 337 cases (at the New York Willard Parker Hospital), or in 24 per cent. Of 33 consecutive cases of rash, 19 were simple erythema, 4 were scarlatiniform, 4 morbilliform, in 13 there was erythema multiforme or urticaria, whilst in some a second rash developed after the ~~diphtheria~~ disappearance of the first but of a different character. The same author states that prior to, or with, the development of the rash a sharp rise of temperature occurred to reach its acme at the time of greatest development of the former, after which it usually declined. Regarding their site, it was noted that the rashes were either local or general, in the former case trifling, about the site of the injection, and occurring on the first and third days. Only in the severe cases were the morbilliform and scarlatiniform varieties observed, and then with much more serious systemic disorder, and, occasionally a desquamation after the style of measles. Developing at the site of inoculation, the rash was in many instances seen to spread rapidly to other parts of the body; its most frequent sites were about the buttocks, abdomen, and chest; less frequently about the wrists, elbows,

and knees. Often the spread of the rash was observed not to be continuous, but to involve several parts of the body widely separated, the face being the least often involved.

~~ied~~ The scarlatiniform eruption is frequently accompanied by severe itching; and is most often seen on the back, upper and lower limbs, and chest - seldom the face. It may, moreover, coexist with the Morbilliform, the latter being usually found on the buttocks, knees, and occasionally the face. The fever and constitutional symptoms accompanying the rash are usually of a mild character, but at times they have been observed to be severe, and the patient to become delirious: Sevestre and Martin (Traité des Malad. de L'Enfance, Paris, 1897) cite interesting examples. It is in the scarlatiniform variety that the patient is especially liable to suffer from general discomforts; the condition is apt likewise to be mistaken for scarlet fever itself. This, however, should not occur when one bears in mind; (1) the evanescent character of the antitoxin rash; (2) the coexistence of other forms of rash; (3) its unusually rapid disappearance and re- appearance; (4) the absence of vomiting; (5) the appearance of the throat - if affected; and (6) the resemblance of the desquamation of the antitoxin rash to that of measles. The absence of catarrhal symptoms and of Kopliks spots should enable the morbilliform antitoxin rash to be recognised as such.

Cause of the Antitoxin Exanthemata.-

It is now regarded as certain (having been proved by experimentation with non - immunized serum) that the horse serum, and not the antitoxin itself, is responsible for the occurrence of the above. It has been noted that the rash is less apt to appear after small doses than large or frequently repeated ones, and that the number and severity of these cases has been markedly reduced by the employment of concentrated serum. Berg (loc. cit.) states that occurrence of rashes can be greatly reduced by filtering the serum through a fine filter to get rid of certain toxalbumins. Others recommend that the serum be heated before use.

Sevestre and Martin (loc. cit.) state that what they term, the "Exanthemata tardis" - or rashes occurring about the twelfth or thirteenth day and accompanied by more or less constitutional disturbance - are most likely due to a streptococcus infection, their theory being based upon the character of the symptoms, - joint affections, etc., - and the fact that in a certain number of observations they have found that these phenomena occur only where there is a mixed diphtheria, or a true strepto - coccie angina, and not in pure diphtheria : the streptococcus may be the sole cause of these phenomena. The 13 days is regarded as the period of incubation of this infectious disease.

Presuming the correctness of their hypothesis these authors conclude that these epiphenomena - rash, joint pains, etc. - are due, first, to a peculiar state of

the organism resulting from the, occurrence of a secondary infection, particularly by streptococci; and, second, the injection of serum which acts as an occasional cause, and in a manner not yet determined.

Joint Affections.-

The occurrence of joint affections has already been mentioned. The pains about the larger joints, following the injection of antitoxin, may be of an excruciating character, the hips, knees, wrists and shoulder being most often affected, and usually one at a time only. The London clinical Society in their report (see before) mention joint pain as occurring in 40 out of 633 cases, at the time of the rash with high temperature, and most often with large injections.

The Metropoliton Asylums Board Report, previously referred to, mention joint pains, in 1895, as occurring in 4.7 per cent of the cases.

The greater the concentration of the serum and the smaller the doses administered the less severe will be the joint pain The latter may be of an excruciating character; is increased by movement, but not by pressure the local symptoms being of a minor kind - slight redness and oedema.

~~Effect of Antitoxin upon the Blood.~~ ~~Ewing ("Clinical Pathology of the Blood", 1901).~~ ~~states that 15 out of 18 cases examined showed a~~

Effect of Antitoxin upon the Blood.

Ewing ("Clinical Pathology of the blood", 1901) states that 15 out of 18 cases examined showed a diminution of leucocytes, especially from 15 to 40

minutes after the injection of antitoxin, and affecting chiefly the faintly staining mononuclear and polynuclear leucocytes. In addition to this the antitoxine was found to have influenced the staining power of the leucocytes: five children in whom this did not take place died. Ewing considers that when the hyperlencocytosis which regularly occurs in diphtheria is not converted into a hypoleucocytosis by the injection of antitoxin a fatal outcome may be expected. A certain amount of diminution in the red cells also occurs, thus accounting for the anaemia seen in children after serumtherapy.

Epiphenomena.-

According to d'Astras ("Effects of serum on the Uterus"- Soc. med. de Hôp., April, 1895, p. 348), antitoxin is possessed of a marked tendency to cause haemorrhage from the uterus, menorrhagia, or premature menstruation.

Occurring from the tenth to the fifteenth day, Sevestre and Martin (loc. cit). have noticed a valvitis in young girls following antitoxin injections; occassionally a fatal diarrhoea with blood in the stools. cases of tetanus have been occasionally observed, due - as are all these epiphenomena - to serum badly prepared.

TRACHEOTOMY AND INTUBATION.

It does not, of course, come within the scope of a medical dissertation such as this to dilate upon the technique of these operations,- both of which are fully described in surgical treatises, - but a few points of special interest to the physician may well receive comment.

TRACHEOTOMY.

Indications for Tracheotomy.-

Tracheotomy is specially indicated: (1) in cases in which, for any reason, intubation cannot be performed; (2) when excessive oedema contra - indicates intubation; (3) when there is a membrane low down the trachea; (4) With extensive involvement of the naso-pharynx, where intubation has failed to give relief; (5) as a measure secondary to intubation.

INTUBATION.

Indications for Intubation.-

In former times intubation was resorted to as soon as laryngeal diphtheria was diagnosed. Now, however, knowing that antitoxin as often as not does away with the necessity for operative interference, it is as well not to intubate until - a second or third dose of serum having been given - symptoms of marked laryngeal stenosis appears, E. 9.: progressive dyspnoea, laboured breathing, retraction of the supra - clavicular and epigastric areas, and a failing pulse. Delay

in these cases is dangerous. The operation must be performed forthwith.

Tracheotomy versus Intubation.-

Presuming the mortality from these operations to be about equal, the advantage of intubation over tracheotomy may be summed up as follows:-

1. It is a bloodless and less ghastly operation, and one not objected to by the patient's relatives.

2. No anaesthetic or trained assistants are required.

3. The operation is performed in a few seconds and requires no preparation for its performance.

4. The patient requires less troublesome after-care.

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WARD IX Chart No. 1 Admitted, Nov: 14th 1903

Name Sidney Thornley
Age 6½ years
Occupation Scholar
Residence Cargle Cottage Leone
Recommender Dr Robertson

DIAGNOSIS.

Diphtheria

TREATMENT.

Diet

Medicine

Fo face p. 2 60

Tinct: digitalis
Liq: Strychnine. th 24
Sp: Chlor 3iv
Mist: Bism 3iii
℥ 3ii 4 hourly

Extras Brandy 3i 4 hourly

Time	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E
Bowels	1	1	1	1	1	2	1	1	2	1	1	1	1	1	1						
Urine		20	20	18	18	28	24	28	28	26	22	20	18	16							
Day of Dis.																					
Pulse,	115 130	120 128	116 112	108 115	92 108	100 108	100	92	112 112	108 120	112 80	98	80 100								
Resp.,	28 30	24 24	24 24	24 26	26 30	28 24	24	24	24 24	24 20	28 32	26	24 24								
Date,	14	15	16	17	18	19	20	21	22	23	24	25	26	27							

Temperature (Fahrenheit): 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
Normal Temperat. of Body

8000 units Strepto-dec. serum
6000 " "
6000 " "
6000 " "
8000 " "
Antistrepto-dec. serum " "
5000 units Strepto-dec. serum

Nov:

Result, Dies 11.20 a.m. 27th Nov: 1903. Dismissed, 190

NOTES OF CASE.

Throat now cleared.

WARD 12. Chart No. 1 Admitted, Apl. 16th 1904

Name Jessie Scott

Age 20 yrs.

Occupation

Residence Pleasant Hill Scone

Recommender Dr Robertson

E

DIAGNOSIS.

Diphtheria

TREATMENT.

Diet Milk only

Medicine Liq: Stroph 3i aq: ad ℥ vi

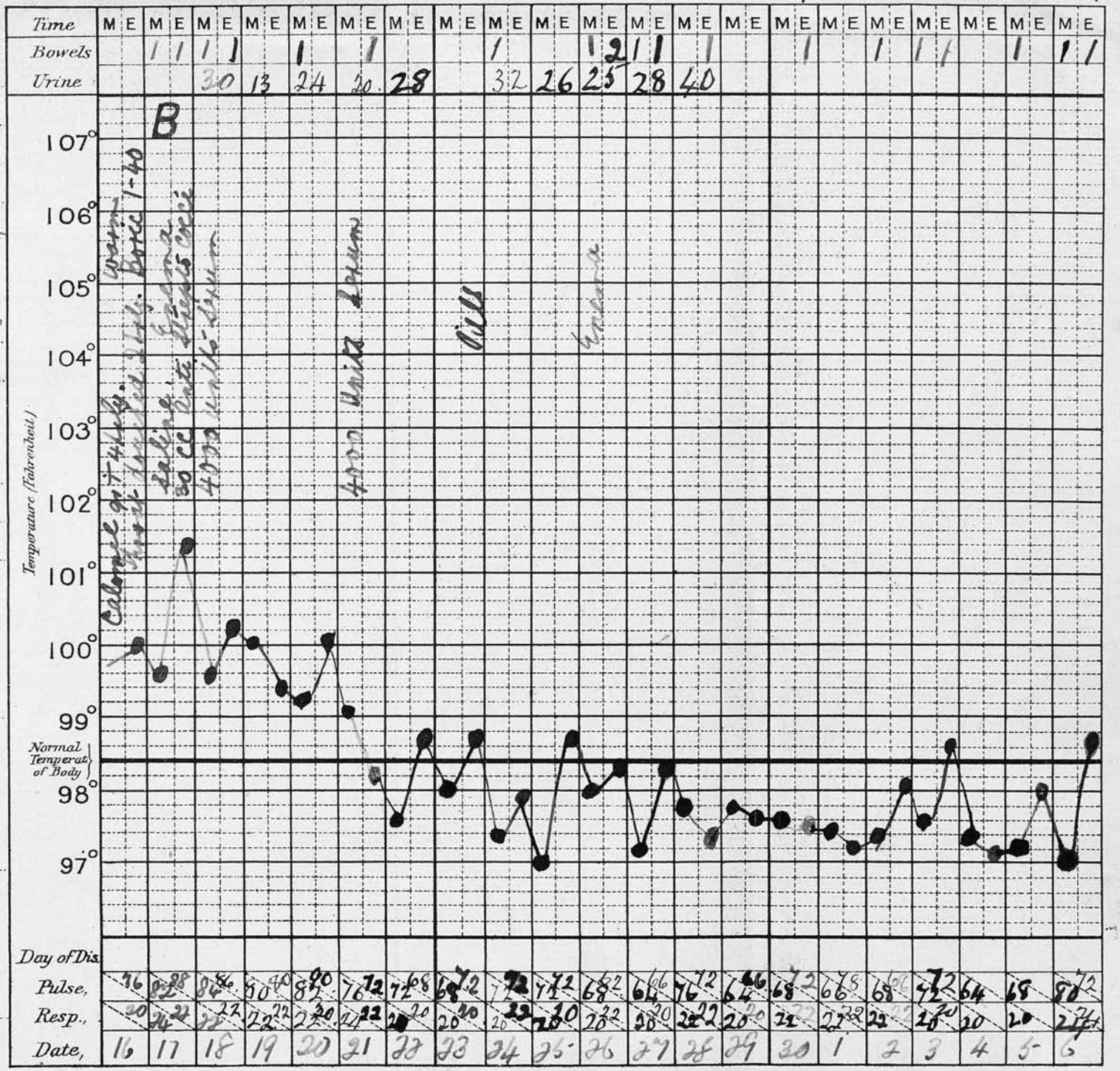
3ss tid

Hy

Tr. Strophan

m 3 tid

Extras



Result,

Dismissed, 190

WARD X Chart No. 2 Admitted, April 16th 1904

Name Jessie Scott
Age 20 years
Occupation
Residence Pickerton Hill Scone
Recommender Dr Robertson

DIAGNOSIS.

Diphtheria

TREATMENT.

Diet Conval.

Medicine Liq. Strych. 3i ad. aq. ad ℥vi 3i T.i.d.

℞ L. Strophan. m. iii T.i.d.

Extras

Time	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E
Bowels		(1			1																				
Urine																									
Day of Dis.																									
Pulse,	76 80	72 88	88 88	80																					
Resp.,	24 24	24 24	22 20	22																					
Date,																									

Temperature (Fahrenheit)

107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

Normal Temperature of Body

Result, Dismissed, 16th May 1904

APPENDIX.

The three temperature charts (two cases) are specially selected by the writer from amongst numerous others in his possession, to illustrate the results obtained from the use of Serumtherapy in his practice.

The chart of the boy Sidney Thornley is of interest in that, firstly, large doses and ultimately a large amount of Antitoxic serum was used without any benefit being derived, and, secondly in view of the sudden fall of temperature occurring with the use of antistreptococcus serum.

As regards the diphthera serum, the writer's experience has been that country people labour under the impression that it is infallible, and in consequence frequently omit to carry out the other necessary general and therapeutic measures recommended, More especially as regards the toilet of the throat and nose.

In the scone Board School the writer had occasion to point out what seemed to him a great source of infection, namely, t he carless handling of children's slates: one child may never have the same slate two days in succession, and the methods of cleaning them are Crude indeed. The propagation of the disease therefore, becomes easy, in view of which both the writer and the Medical Officer of Health drew attention to the desirability of having the slates regularly cleaned and disinfected, so also the school books and o

other furnishings which the children may have occasion to handle.

Whilst not claiming any specific action for tincture of the perchloride of iron - the former popularity of which has been noted already - the writer has satisfied himself, from an extensive experience, as to its efficacy when given with quinine, chlorate of potash, and glycerine.

FINIS.